TABLE V

NONSMOKER EXPOSURE TO ETS
RECENT WORKPLACE AIR MONITORING STUDIES: NICOTINE AND RESPIRABLE PARTICLES*

Study	Sample	Nonsmoker Exposure; (Mean; ug/m^3)	Comment
Hedge, et al. (1993) USA	27 office buildings Area sampling	2.4 ug/m^3 - nicotine 10.2 ug/m^3 - RSP/UVPM**, ***	Smoking restricted to offices and open-pla cubicle workstations; ("a nonsmoker may be exposed to the nicotine content of about 3 cigarettes per year.")
" "		3.8 ug/m^3 - nicotine 5.8 ug/m^3 - RSP/UVPM	Smoking restricted to areas with no local treatment of air; ("[nonsmoker exposure equivalent of] about 5 cigarettes per year.")
Lambert, et al. (1993) USA	7 restaurants	1.0 ug/m^3 - nicotine 27.8 ug/m^3 - RSP	Median levels for nonsmoking sections.
Broder, et al. (1993) Canada	3 office buildings	23 ug/m^3 - RSP 14 ug/m^3 - RSP	Before smoking ban. After smoking ban.
Holcomb (1993)	5 studies; 270 samples, offices and public buildings	0.3 ug/m^3 - nicotine	Review article.
	24 studies; 640 samples, offices and public buildings	45.9 ug/m^3 - RSP	
Turner, et al. (1992) USA	585 offices	0.17 ug/m^3 - nicotine 20.11 ug/m^3 - RSP	254 nonsmoking offices; ("Spillover from smoking areas to nonsmoking areas appears t be minimal.")
Guerin, et al. (1992)	Review of published nicotine data for offices, restaurants, public buildings and transportation facilities		"Nicotine concentrations are generally at least one and up to three orders of magnituc lower than the eight hour time-weighted permissible exposure limit of 500 ug/m^3 specified by OSHA for workplace exposure."
Oldaker, et al. (1992) USA	4 office buildings	2.75 ug/m^3 - nicotine 21 ug/m^3 - RSP/UVPM	Unrestricted smoking (2 buildings).

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* Studies include 700 offices and 150 restaurants that were not considered in OSHA's proposed rule on ETS.

** RSP = respirable suspended particulate; UVPM = ultra-violet particulate matter (identifies ETS contribution to indoor levels of RSP).

*** OSHA's permissible exposure limit (PEL) for nicotine is 500 ug/m^3; the PEL for respirable particulate is 5,000 ug/m^3.

Study	Sample	Nonsmoker Exposure; (Mean; ug/m^3)	Comment
Oldaker, et al. (1990) USA	125 offices	4.8 ug/m^3 - nicotine 27 ug/m^3 - RSP/UVPM	Average for both smoking and nonsmoking areas.
" "	82 restaurants	5.1 ug/m^3 - nicotine 36 ug/m^3 - RSP/UVPM	Average for both smoking and nonsmoking areas. "Estimated mean exposure for an eight-hour day in an office is 0.02 cigarette equivalent and for a 1-L meal in a restaurant, 0.003 cigarette equivalent."
Vaughan and Hammond (1990) USA	Office building 80 sample locations	2.0 ug/m^3 - nicotine 0.3 ug/m^3 - nicotine	Before smoking restrictions. After smoking restrictions.
Crouse, et al. (1989) USA	42 restaurants	5.9 ug/m^3 - nicotine 26.1 ug/m^3 - RSP/UVPM	"Average exposure to ETS is 50 to 1,000 times lower than exposure [to] a single cigarette."
Proctor, et al. (1989) UK	Office building 10 samples	0.6 ug/m^3 - nicotine 8.8 ug/m^3 - RSP/UVPM	Median levels.
Thompson, et al. (1989) USA	35 restaurants 6 food courts Personal nicotine monitor	5.4 ug/m^3 - nicotine 2.3 ug/m^3 - nicotine	Overall exposure.
Carson and Erikson (1988) Canada	31 offices	7.2 ug/m^3 - nicotine**** 24 ug/m^3 - RSP/UVPM	"Exposure estimated from mean nicotine and UV-PM results were 0.004 and 0.001 cigarette equivalent per hour, respectively."
Sterling and Mueller (1988) Canada	Office building 8 nonsmoking locations receiving recirculated air from a designated smoking area	1.0 ug/m^3 - nicotine 8 ug/m^3 - RSP	"Equivalent to 1/1800 of the nicotine [per hour] inhaled by actively smoking one cigarette."

**** Incorrectly cited in the OSHA NPR.

submitted to the docket of the OSHA RFI on Indoor Air in 1992. (Ex. 3-1074)

The studies on ambient measures of nicotine in offices and restaurants that were omitted from OSHA's analysis report average levels of approximately 2.0 and 3.5 ug/m^3 nicotine, respectively. These exposures are equivalent to 1/400 to 1/200 of the nicotine found in a single cigarette. Averages for nonsmoking areas in workplaces with smoking restrictions are even lower, averaging less than 1 ug/m^3 nicotine, or about 1/1,000 of the nicotine in a single cigarette. This means that the typical nonsmoking worker would have to spend from 200 to more than 1,000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of a single cigarette.[26,31,32,35-36] Moreover, these exposures are 100 times lower than OSHA's PEL for nicotine, 0.5 mg/m^3. (29 CFR 1910.1000, Table Z-1)

Respirable suspended particles (RSP) are contributed by a number of sources, a point acknowledged in the Proposed Rule. (59 FR 16003) OSHA states:

> People contribute millions of particles to the indoor air primarily through the shedding of skin scales. Many of these scales carry microbes, most of which are short-lived and harmless. Clothing, furnishings, draperies, carpets, etc. contribute fibers and other fragments. Cleaning processes, sweeping, vacuuming, dusting normally remove the larger

particles, but often increase the airborne concentrations of the smaller particles. Cooking, broiling, grilling, gas and oil burning, smoking, coal and wood generate vast numbers of airborne indoor pollutants in various classifications.

Results of a 1993 study on particle exposures conducted by the U.S. EPA indicate that one hour of cooking activity generates approximately 100 times the particle concentration from a single cigarette.[39] The study reported that average percent contributions from "fine particle mass" (RSP) were: 10 percent from smoking, 68 percent from outdoor sources and 22 percent from unidentified sources.[39]

Special methods have been developed for the analysis of airborne particles that determine the relative contribution of ETS to total particles in the indoor air. One analytic technique employs ultraviolet particulate matter (UV-PM) as an indicator of the particle fraction contributed to the air by ETS.[8] Studies of UV-PM measurements in offices report ranges of from 27 to 44 ug/m^3 in areas where smoking is permitted.[24] Although indoor exposure limits do not exist for ETS-related particles, the World Health Organization (1992) has designated 100 ug/m^3 or less as an exposure level of "limited or no concern" for particles contributed by ETS.[40]

A recent review has summarized average levels of airborne particles from smoking and nonsmoking areas reported in studies

performed in various settings.[24] The average particle concentration in the air of homes with smokers is about 27 micrograms per cubic meter higher than in homes of nonsmokers; offices and public places that permit smoking report average levels of particles that are about 22 micrograms/cubic meter higher than those reported for nonsmoking locations, and smoking areas of restaurants report levels that are 42 micrograms/cubic meter higher, on average, than nonsmoking areas.

In the largest single study of its kind, researchers monitored 585 offices for various ETS-related constituents, including particles.[29] The average level of particles recorded for 331 offices in which smoking was permitted was <u>46 ug/m³</u>, compared with an average of <u>20 ug/m³</u> for 254 nonsmoking offices. These levels are all far below that designated by the WHO as "limited or no concern."[40]

The Proposed Rule contends that the contribution of RSP by smoking is much greater than that reported in studies employing the UV-PM method. The Proposed Rule combines the results of three studies of smoking and nonsmoking buildings conducted in the early 1980s. The combination of data from the three studies provides an average estimate of <u>262 ug/m³</u> RSP in smoking buildings, compared with <u>36 ug/m³</u> in nonsmoking buildings. (59 FR 15990) An analysis identical to that presented in the Proposed Rule occurs in a 1992

paper written by two antismoking activists.[41] (The paper, however, is not referenced in the Proposed Rule.) Careful examination of the three studies cited reveals that the data therein do not support the contention of the Proposed Rule. One of the studies measured RSP levels in pizzerias, bars, lodge halls, bowling alleys, church bingo games and fast food restaurants in 1980. The only office measurement reported was conducted under experimental conditions in a room in which levels of ETS were generated by seven smokers smoking 32 cigarettes in 49 minutes, yielding RSP values as high as 500 micrograms per cubic meter. One of the other studies cited included no office measurements. Such selective combinations of data only serve to confuse the issue. The studies clearly do not represent typical workplaces at 1994 levels of ETS exposure.

According to a comprehensive review undertaken by researchers at Oak Ridge National Laboratories, "chemical means for estimating the contribution of ETS to RSP have been evaluated, and suggest that ETS-RSP may comprise from 10 percent to 50 percent of indoor air RSP, in the field scenarios to which the methods have been applied."[8] Indeed, even a cursory examination of actual studies, consisting of hundreds of office, restaurant and other workplace situations, reveals that source-apportioned RSP levels due to ETS are at levels 5 to 10 times lower than those suggested in OSHA's Proposed Rule.[24, 29, 31-33]

ETS constituent levels in the workplace: an interpretation

With the exception of nicotine, solanesol and 3-ethenylpyridine, none of the substances used as markers for ETS in the air is characteristic of tobacco smoke. Other sources such as heaters, stoves, building materials, cleaning products and human activities often generate greater levels of those substances than ETS.[8] For example, studies indicate that automobile combustion, industrial processes, home heating and gas cooking are the predominant sources of carbon monoxide and nitrogen oxides in indoor air.[24] For this reason, neither constituent is an appropriate marker for ETS. Researchers report that there is little difference in ambient levels of carbon monoxide or nitrogen oxides in smoking and nonsmoking areas of workplaces and public places and in homes with or without smokers.[8,24,42-46] Levels of volatile organic compounds such as formaldehyde and benzene in the presence of smoking are often indistinguishable from levels reported in nonsmoking areas.[8,32,47-51] Studies that have examined ETS constituent levels of nitrosamines[52-54] also report minimal contributions to overall ambient air levels in homes, offices and public places.

Nicotine and RSP were selected by OSHA as the most suitable markers for assessing exposure to ETS. While nicotine is characteristic of tobacco smoke in the ambient air, it represents

a gas-phase constituent and indicates nothing about the particle (RSP) phase of environmental tobacco smoke exposures. RSP, on the other hand, is not characteristic of tobacco smoke, but, if correctly sampled and analyzed, can provide approximations of exposure to the particle phase of ETS. Measurements of both nicotine and RSP are typically reported in terms of micrograms per cubic meter (ug/m^3). The absolute values of the levels measured, however, may not be meaningful to anyone other than scientifically trained personnel. It is therefore convenient to refer to a comparative or illustrative device in order to facilitate understanding about the levels of exposure to nicotine and RSP as reported in the scientific literature.

One particularly useful illustrative means for representing reported levels of nicotine and RSP in the ambient air is the notion of "cigarette equivalents." The use of "cigarette equivalents" as a heuristic device for understanding ETS exposures does not imply that active smoking and nonsmoker exposure to ETS are the same thing, or that mainstream smoke is "equivalent" to ETS. Nor does it mean that a measure of nicotine or RSP in terms of "cigarette equivalents" represents exposure to other constituents in ETS. However, the concept of "cigarette equivalents" offers a convenient means for quantitative comparisons of ETS exposures, and is a commonly used method for reporting measured levels in the published literature.[24, 26, 31, 32, 36, 55]

For example, Oldaker, et al. reported average levels of nicotine exposure of 4.8 ug/m^3 for 125 offices.[31] The authors estimated exposures to nicotine for an eight-hour work day in an office to be equivalent to 0.02 of a cigarette. The authors also measured nicotine levels in 82 restaurants and the resulting average concentration was 5.1 ug/m^3; the exposure equivalent for a one-hour meal was 0.003 of a cigarette.

Carson and Erikson, cited in OSHA's Proposed Rule (59 FR 15991), measured nicotine and RSP (UV-PM) in 31 offices.[55] The authors wrote: "Exposure estimated from mean nicotine and UV-PM results were 0.004 and 0.001 cigarette equivalent per hour, respectively." Proctor measured nicotine levels in smokers offices and reported that the average level of 3.1 ug/m^3 nicotine would provide an exposure equivalent of 0.018 to 0.010 of a cigarette over the course of a work-day.[32] Proctor writes: "This means that a male nonsmoker would have to work in the smoker's office for over 11 weeks before being exposed to the equivalent nicotine as from smoking one cigarette." UV-PM/RSP levels in smokers' offices were reported at 24 ug/m^3.[32] This would translate into an exposure equivalent of 0.013 cigarettes per day. Thus, Proctor writes: "This again would result in a male nonsmoker working in the smoker's office for 15 weeks before being exposed to the equivalent particulates as smoking one cigarette."

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Hinds and First, in one of the first studies of its kind, measured nicotine levels in various public places in 1975.[36] The venues included waiting rooms, restaurants, and cocktail lounges. Measured levels of nicotine ranged from 1.0 to 10.3 ug/m^3, translating into equivalents of 0.001 to 0.009 cigarette per hour.

In 1993, Hedge, et al. measured nicotine in 27 air-conditioned offices under various smoking policies.[26] The authors write: "[A] nonsmoking office worker in open offices who does not spend time in designated smoking areas on average may be exposed to the nicotine content of about three cigarettes per year."

Although a suitable internal dose marker for ETS is not available, scientists have estimated that ETS-related particle uptake in the typical nonsmoker is approximately two-hundredths of one percent (0.02 percent) that of the active smoker.[56-58] Other scientists have estimated that ETS "inhaled doses" (based on particles) are 10,000 to 100,000-fold less than average doses calculated for active smokers.[59] The estimated nonsmoker "dose" is equivalent to actively smoking less than one cigarette over the course of a year.

Another scientist recently calculated estimated "retained doses" for nonsmokers using average exposures to various ETS constituents reported in the published literature.[24] The calculated

dose for tobacco smoke particles, expressed in terms of cigarette equivalents, ranges from less than one-half to about four cigarettes per year for "light" and "heavily-exposed" nonsmokers, respectively.

> **The Proposed Rule does not utilize actual ambient exposure measures for ETS in the workplace in its determination of "significant risk"; exposure estimates from epidemiologic studies on ETS are used in the determination of "significant risk"; exposure estimates from epidemiologic studies are not quantifiable; they are unreliable and inconsistent with actual ambient measurements of ETS**

In its analysis of "significant risk" for ETS, OSHA employs two epidemiologic studies on lung cancer and heart disease in nonsmokers. (Exs. 8-106, 8-139) (59 FR 15995) Exposures to ETS were determined in those studies through the use of questionnaires that, in turn, were dependent upon the accuracy of recall of exposure among those questioned. No actual ambient exposure measures were included in the epidemiologic studies. **OSHA's entire discussion of ambient measures of ETS exposures in the workplace is omitted from its significant risk analysis and replaced by the exposure estimates from two epidemiologic studies on nonsmoker lung cancer and heart disease.**

One critical source of bias in epidemiologic studies on ETS is called "exposure misclassification bias" and arises from

errors in reporting ETS exposures.[15,60-65] As was suggested earlier, epidemiologic studies do not measure actual ETS exposures, but rather employ questionnaires to generate estimates of ETS exposure over long periods of time. Sometimes, the studies use exposure estimates given by spouses, children, or next-of-kin. The questionnaires used in epidemiologic studies on ETS vary and have not been validated or checked for accuracy. The National Research Council and other authors have criticized the use of questionnaires as representations of accurate and comprehensive exposure histories in ETS studies.[66,67] Other studies demonstrate that questionnaires are an unreliable and inaccurate measure of ETS exposure.[14-16,68-69]

Typically, questions regarding ETS exposures in epidemiologic studies are of the following sort: "Are you married to a smoker?"; "How long have you lived with a smoker?"; "About how many cigarettes a day did the smoker smoke in your presence?"; "About how many cigarettes a day did the smoker smoke?"; etc. Answers to such questions vary widely across studies. For example, Friedman, et al. noted that, in their study, 30 to 35 percent of nonsmokers who were married to smokers reported no exposure whatsoever to ETS.[15] A more recent study reported a 36 percent exposure misclassification rate when ETS exposures determined by questionnaires were compared to exposures determined by ambient air measurements.[16] The authors of that study conclude: "The results . . . suggest that questionnaires lead to a large amount of

misclassification which must be taken into account when assessing the effect of ETS exposure" and that "an objective method to measure exposure which is sensitive, accurate, and reliable is needed to validate them." Another recent study that compared ETS measurements with questionnaire responses found that "the false report rate was high. Among those 575 participants reporting an average of 42 or more hours/week [exposure to ETS], 58 percent did not have a detectable cotinine level."[68]

Coultas, et al., in a study cited in the Proposed Rule (Ex. 8-66), report that "the levels of cotinine, respirable particles, and nicotine varied widely with self-reports of exposure to ETS."[12] A second study by Coultas, et al. reports that "personal exposure also varies with the nonsmoker's proximity to the smoker. Questionnaires cannot comprehensively and accurately assess each of these factors. Not surprisingly, we found that the questionnaire responses were poor predictors of concentrations of respirable particles and nicotine."[13] Schenker, et al., in another exposure assessment study, concluded that "self-reported exposure to ETS is an inaccurate measure of passive smoking in the occupational setting."[63]

Pron, et al. noted in their study that "responses to initial screening questions used to detect a person's exposure to passive smoke were more reliable for residential than for

occupational exposure . . . [Q]uantitative measures of exposure to passive smoke, i.e., number and duration of exposure, were even less reliably reported."[62] In another study by Coultas, et al., the authors reported that "responses concerning recent tobacco smoke exposure and urinary cotinine levels were correlated only to a modest degree." The authors "conclude that adults can reliably report whether household members smoked during their childhood, but information on quantitative aspects of smoking is reported less reliably."[69] Lerchen and Samet in 1986 reported that spouses of smokers correctly reported the smoking status of their spouses, however, "for the number of cigarettes smoked per day, wives tended to report 20 cigarettes smoked even when their husband smokes substantially more or less."[64]

OSHA argues, within the context of its analysis of "significant risk" for ETS, that home "exposures" to ETS are comparable to workplace exposures. It is argued that "in the absence of purely occupational data, information derived in environments other than worksites is also considered." (59 FR 15994) The Proposed Rule cites a report prepared by Meridian Research in 1988 that contends that "it is the exposure to environmental tobacco smoke, and not the environment in which that exposure occurs, that is the important risk factor." (Ex. 8-221) The Proposed Rule continues: "Therefore, health effects observed and the risk estimates calculated from studies of the general

population, or of selected subgroups, such as nonsmoking wives of smoking husbands, are relevant to the working nonsmoking population." (59 FR 15994)

There are at least three distinct issues regarding OSHA's argument. First, OSHA equivocates on the phrase "exposure data." OSHA proposes to replace actual ambient air measures of ETS constituents in the workplace with exposures assessed by questionnaire response in epidemiologic studies. The foregoing analysis clearly indicates that questionnaire responses cannot quantitatively approximate, much less replace, actual measures of ETS constituents in the air of workplaces.

The second issue raised in OSHA's argument concerns the comparability of actual levels of ETS constituents in the home and in the workplace. OSHA contends (but does not prove) that the levels are comparable. (59 FR 15994) Recent data, however, indicate that this is not the case. In a 1993 study of 96 nonsmoking, married women, ETS exposures were continuously monitored over a one-week period.[70] The results for actual measures of ETS exposures (using 3-ethenylpyridine and nicotine as markers for ETS) indicate that workplace exposure is "tenfold lower than home exposure due to living with a smoker." Average values for exposure to nicotine in the workplace indicate that it is a trivial source of (ETS) exposure (median value, 0.21 ug/m^3 nicotine,

compared to the nicotine delivery of a single cigarette: 880 ug/m^3).[70]

The third issue raised in OSHA's argument is whether or not data from household "exposures" to ETS can be applied to the workplace. If current published data regarding workplace exposure to ETS constituents were not available, then perhaps OSHA could make its argument. However, current workplace exposure data are available, including seven major studies and two major review surveys of ETS measurements in workplaces, that could have been used by OSHA in its analysis. It is clear that OSHA chose not to use the data from those studies and reviews because, in most instances, the data reveal that ETS exposures in the workplace are minimal and often indistinguishable from background levels. Even in the complete absence of appropriate data on ETS measurements in the workplace, OSHA would still have to justify its argument for the application of exposure data from epidemiologic studies in the home to the workplace. As one scientist notes:

> Because workers not exposed to ETS and workers exposed to ETS in the same occupational group have not been medically followed for several years, there is no justification to apply the reasoning that because home exposure through spousal smoking might be associated with cardiopulmonary disease, then workplace ETS exposure can be expected to have a similar association . . . . Results of household exposure cannot be applied to workers . . . . Confounding factors related to ETS exposure in workplaces are different from factors

influencing spouses and children in studies of household exposure. Dietary factors and household pollution may influence the incidents of spousal and childhood diseases. On the other hand, workers are exposed to industrial chemicals and outdoor pollutants as well as work-related stress. Familial patterns of inherited or acquired susceptibility to cardiopulmonary disease do not apply to occupational groups . . . . Unlike household exposure, workplace exposure can be monitored by good industrial hygiene practice.[2]

Recent data on ETS exposures in the workplace based upon personal monitoring of ETS constituents undermine OSHA's assumptions regarding the extent and frequency of ETS exposures, the comparability of home and workplace ETS exposure levels, the ineffectiveness of dilution ventilation for the minimization of ETS exposures and the accuracy of questionnaires and biomarkers for the quantitation of ETS exposures

The results from three recent independent studies on personal exposures to ETS in the workplace are now publicly available. The first study, conducted by indoor air quality specialists from British Columbia, Canada, assessed personal exposures to ETS constituents among 25 nonsmoking subjects in two office buildings in Richmond, Virginia.[71] The personal monitors recorded levels of exposure to four indicators of particle-phase ETS and two constituents of vapor-phase ETS, including nicotine. Smoking was unrestricted throughout the buildings and the

ventilation systems were operated in accordance with the outdoor air ventilation rates specified in ASHRAE Standard 62-1989. Approximately 20 percent of the total workforce in the two buildings were active smokers.

Average exposures to total respirable suspended particulate ranged from 23 to 29 ug/m^3; the average range for nicotine concentrations was 2.04 to 2.71 ug/m^3. Correlations among cotinine levels, questionnaire responses regarding the frequency of smoking and measured levels of particle and vapor-phase indicators were very weak, suggesting that both questionnaire responses and the use of cotinine are poor surrogates for quantitating exposures to ETS constituents. Measured exposure levels of particle and vapor-phase constituents in this study were two to three times lower than levels estimated in OSHA's Proposed Rule.

Researchers from Oak Ridge National Laboratories reported preliminary results from an on-going study of personal exposures to ETS in May, 1994.[72] Participants in the study wore personal sampling pumps that collected various ETS particle and vapor-phase constituents. The samplers were operated during work hours and in all locations away from work. Preliminary results indicate that the range of average respirable suspended particulate levels in the workplace was from 10 to 30 ug/m^3; average nicotine levels ranged between 0.05 and 0.1 ug/m^3. Median time-averaged exposure levels

for respirable suspended particulate and nicotine in a smoking workplace were 20.8 ug/m^3 and 0.243 ug/m^3, respectively. For the nonsmoking workplace, average RSP exposure levels were 15.1 ug/m^3 and average nicotine levels were 0.034 ug/m^3.

Time-averaged exposure levels of nicotine in a smoking home were 4.35 times higher than average levels reported for workplaces in which smoking was permitted (0.827 vs. 0.190 ug/m^3).[72] Measurements of ETS-related particles (UVPM, FPM, and solanesol) indicated nearly three times the exposure in a smoking home compared to a smoking workplace, even though all the absolute values of the ETS-related particles were low. Average salivary cotinine levels did not effectively separate individuals who lived in a nonsmoking home and who worked in a smoking workplace, and individuals from a nonsmoking home and nonsmoking workplace (0.36 vs. 0.11 ng/mL).

A similar study conducted in the United Kingdom by researchers from Hazelton Laboratories was completed in 1993. Two hundred and fifty-five participants were monitored for personal exposures to ETS vapor-phase and particle-phase constituents.[73] Average levels of ETS constituent exposure were low -- over five times lower than the levels estimated in OSHA's Proposed Rule (e.g., seventy percent of the subjects were exposed to less than 10

ug/m^3 of ETS-related particles and over 60 percent were exposed to less than 1 ug/m^3 of nicotine).

The Hazelton researchers also ranked relative contributions of ETS constituents from work, home, travel and leisure locations. Data gathered through questionnaires about relative contributions of ETS from each venue were compared with actual measures of ETS constituents. The results indicate that subjective estimates of exposure tended to rank as higher the relative contributions of ETS from leisure, work, home and travel, respectively. Direct ambient air measurements indicated that the ranking of relative contributions to total ETS exposure was: the home, leisure venues, work and travel. Subjective assessments appeared to overestimate contributions of ETS from both workplace and leisure venues.

Mean exposure levels for various ETS constituents were greater for subjects with a smoking spouse or partner than for those with a nonsmoking spouse or partner, but the distribution of the results did not provide a clear distinction between the two groups. Forty-six percent of subjects with a smoking spouse or partner assessed their ETS exposure as "none" or "low." This assessment was supported by direct ambient measurements. Approximately 30 percent of subjects with a smoking spouse or

partner assessed leisure or work as their principal source of exposure.

The final objective of the study was to compare questionnaire responses, direct ambient air measurements and salivary cotinine levels as methods for assessing exposure to ETS. Direct measurements by personal monitoring appeared to provide the most reliable overall estimates of ETS exposures. The data indicate that salivary cotinine levels correlated very poorly with direct ambient air measurements of ETS constituents. Some subjects who had been exposed to high levels of ETS-related particulate and nicotine had no detectable salivary cotinine levels, and some subjects who had not been exposed to any measurable quantity of ambient nicotine had relatively high levels of salivary cotinine.

The TDSA, Oak Ridge and Hazelton studies demonstrate the viability and accuracy of personal monitoring for ETS constituents. The studies reaffirm the inaccuracies inherent in the use of questionnaires and cotinine for the quantitative assessment of ETS exposures. The overall results indicate relatively low contributions of ETS-related constituents to total pollutant burdens for individuals exposed to tobacco smoke in the workplace. The data tend to undermine the claims that ETS exposures are "ubiquitous" and that levels of ETS encountered at work are comparable to levels encountered in other venues.

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SECTION V

MATERIAL IMPAIRMENT: LUNG CANCER

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LUNG CANCER

OSHA'S PROPOSED RULE FAILS TO DEMONSTRATE THAT CURRENT ETS EXPOSURES IN THE WORKPLACE POSE A SIGNIFICANT RISK OF MATERIAL HEALTH IMPAIRMENT DUE TO LUNG CANCER IN EXPOSED WORKERS

At Section II.C.6.(a), OSHA's Proposed Rule claims that the "results of epidemiological and experimental studies indicate that exposure to ETS is causally associated with cancer of the lung in chronically-exposed nonsmokers." (59 FR 15979) At Sections IV.A. through IV.D. (59 FR 15992-15996), OSHA then proceeds to conduct a "Preliminary Quantitative Risk Assessment" for lung cancer.

However, OSHA's Proposed Rule fails to provide adequate support for the claim of a causal association, or to validate the decision to conduct a risk assessment. OSHA focuses inappropriately on data on "spousal smoking," rather than considering in full the available epidemiologic data on ETS exposures in the workplace. Moreover, OSHA's review of the scientific literature relevant to this issue is incomplete and inaccurate, as presented in the text, sometimes including misrepresentations of the results and conclusions of certain studies.

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Due to its failure to focus on the best available data on workplace ETS exposures and to its numerous errors and omissions, OSHA's Proposed Rule does not adequately demonstrate a significant risk of material health impairment due to lung cancer in persons exposed to ETS in the workplace.

OSHA FAILS ADEQUATELY TO SUPPORT THE POSITION THAT ETS EXPOSURE IN THE WORKPLACE IS CAUSALLY ASSOCIATED WITH LUNG CANCER IN NONSMOKERS

At Section II.C.6.(a) (59 FR 15979), OSHA claims that data from epidemiologic studies, "taken in the aggregate," support a causal association between ETS exposure and nonsmoker lung cancer. OSHA does not provide references in support of this claim.

In subsequent text, OSHA references the 1992 EPA Risk Assessment on ETS (Ex. 8-311) for that report's discussion of active smoking studies. OSHA invokes the argument of "biological plausibility," suggesting that unspecified qualitative similarities between mainstream smoke and ETS support an analysis of cancer risk due to exposure to the latter. This argument does not withstand critical analysis, such as recognition of the distinct chemical differences among mainstream smoke, sidestream smoke, and ETS detailed elsewhere in this submission. OSHA's failure to

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differentiate among different forms of tobacco smoke pervades this section of the Proposed Rule.

The EPA Risk Assessment on ETS suggested that, because mainstream smoke reportedly contains over 40 "known" or "suspect" carcinogens, so must ETS. (Ex. 8-311) However, the EPA's claim is not convincingly supported by scientific data. The EPA concedes in its report that specific substances responsible for the supposed carcinogenicity of mainstream smoke have never been identified, and that associations between "suspect" carcinogens in mainstream smoke and specific diseases have never been established.

Moreover, most of the claimed "carcinogens" in mainstream smoke have never been tested via inhalation in animals (nickel and polonium-210 have reportedly produced human-type lung tumors in animal studies, but these substances are derived from a number of sources).[1,2,3]

To further support its claim of biologic plausibility, OSHA references a study by the Centers for Disease Control, which reported that cotinine, a metabolite of nicotine, was detected in samples of bodily fluids of all the persons surveyed in the study. (Ex. 8-50) OSHA interprets these reported results as "indicating that everyone in the sample had detectable exposure to tobacco smoke." (59 FR 15980) It is an oversimplification to assume that

any detectable level of cotinine in bodily fluids necessarily implies exposure to tobacco smoke. Nicotine is also present in several foods (potatoes, tomatoes, eggplant, tea); detectable cotinine levels may be produced following the ingestion of reasonable amounts of these foods.[4,5,6] At the sensitive levels of detection employed in the CDC paper (to 0.030 ng/mL), cotinine related to dietary nicotine could certainly be detected. Therefore, any extrapolation of these reported results to the classification of persons as "exposed" to ETS should take diet into account, rather than immediately presuming that detectable cotinine must be due to ETS exposure.

OSHA'S RELIANCE ON DATA ON "SPOUSAL SMOKING" IS INAPPROPRIATE; OSHA FAILS TO DISCUSS RELEVANT AVAILABLE DATA ON REPORTED WORKPLACE ETS EXPOSURES IN THE WORKPLACE

In Section II.C.6.(b), OSHA states that there are "at least 32" epidemiologic studies relevant to a discussion of ETS and lung cancer. OSHA fails to note that the approximately 35 studies publicly available primarily deal with household exposure, assessed most commonly as "spousal smoking." Fourteen studies provide data on reported workplace exposures, which are directly relevant to OSHA's jurisdiction; however, OSHA fails to discuss the workplace data in their entirety.

Taken as a whole, the data on ETS exposures in the workplace do not support a conclusion of increased lung cancer risk

As OSHA's jurisdiction is the workplace, not the home, the spousal smoking data are not the best available data for OSHA to use in promulgating its Proposed Rule. While OSHA erroneously characterizes the spousal smoking studies as studies of "nonsmoking housewives" (59 FR 15993), not all the women included in the studies were "housewives"; in fact, a number of the studies cited by OSHA report estimates of lung cancer risk for workplace ETS exposure. (Exs. 8-36, 8-47, 8-106, 8-119, 8-164, 8-171, 8-192, 8-283, 8-292, 8-326) Additional workplace data are found in studies not referenced by OSHA.[7-9]

The availability of risk estimates for workplace exposure was pointed out to OSHA in Philip Morris' submission to Docket H-122 in response to OSHA's Request for Information on Indoor Air (Ex. 3-1074, response to question 2(a)iii), and in a number of other submissions to Docket H-122. (e.g., Exs. 3-331, 3-1067, 3-1073) While those submissions present detailed discussions of the workplace data, a restatement of the available workplace data is nevertheless presented here. This discussion also includes studies that have appeared since the RFI docket closed.

Of the 14 epidemiologic studies on spousal smoking which include an estimate of workplace ETS exposure, nine were performed in the United States, two in European countries and three in Asian countries. The following are brief descriptions of these studies (in alphabetical order) and their conclusions regarding workplace ETS exposure. Relevant information about the studies (sample sizes, gender of study participants, definition of exposure, the reported point (risk) estimates for workplace ETS exposure, and the statistical significance of the point estimates) are summarized in Table 1.

In a study published in 1992, Brownson and colleagues reported on results of a case-control study of Missouri women who were lifetime nonsmokers or former smokers. (Ex. 8-36) This study is notable for its large sample size, as over 600 lung cancer cases were enrolled, more than 400 of whom were self-reported lifetime nonsmokers. The authors wrote:

> In general, there was no elevated lung cancer risk associated with passive smoke exposure in the workplace (not shown in table). Only lifetime nonsmokers showed a slight increase in risk at the highest quartile of workplace exposure (OR = 1.2; 95% CI = 0.9, 1.7).

As the above paragraph indicates, these authors failed to present their overall risk estimate for workplace smoking, which was apparently not statistically significant. The risk estimate that

TABLE 1: ESTIMATES OF WORKPLACE ETS EXPOSURE AND LUNG CANCER RISK IN NONSMOKERS

STUDY	COUNTRY	NUMBER OF CASES/CONTROLS IN WORKPLACE ANALYSIS	GENDER	EXPOSURE DEFINITION	RISK ESTIMATES
Brownson, et al., 1992	USA	not presented (432/1402 total)	female	"highest quartile" of workplace exposure exposure in the workplace	1.2 (0.9-1.7) "no elevated lung cancer risk"
Butler, 1988	USA	6 cases 7 cases	female male	worked with smoker for 11+ yr worked with smoker for 11+ yr	1.47 (0.15-14.06) 1.72 (0.33-9.04)
Fontham, et al., 1994	USA	609/1247	female	ever exposed	1.39 (1.11-1.74) *
Garfinkel, et al., 1985	USA	14/52 34/118	female	exposure in last 5 years exposure in last 25 years	0.88 (0.66-1.18) 0.93 (0.73-1.18)
Janerich, et al., 1990	USA	not presented (191/191 total)	both	150 person-years exposure	0.91 (0.80-1.04)
Kabat & Wynder, 1984	USA	53/53 25/25	female male	current regular exposure current regular exposure	0.68 (0.32-1.47)[1,2] 3.27 (1.01-10.6)[1,2] *
Kabat, 1990	USA	44/111 37/105	female male	ever exposed at work ever exposed at work	1.00 (0.49-2.06) 0.98 (0.46-2.10)
Kalandidi, et al., 1990	Greece	65/78 (est.)	female	"between extreme quartiles" of exposure some v. minimal exposure exposed at work	1.08 (0.24-4.87) 1.70 (0.69-4.18)[2] 1.39 (0.76-2.54)[1]
Koo, et al., 1984	Hong Kong	2/4	female	exposed at workplace	0.91 (not given)
Lee, et al., 1986	Great Britain	15/158 10/59	female male	ever exposed ever exposed	0.63 (0.17-2.33)[1,2] 1.61 (0.39-6.60)[1,2]
Shimizu, et al., 1988	Japan	not presented (90/163 total)	female	someone at workplace smokes	1.2 (not given) 1.2 (0.70-2.04)[2] 1.2 (0.69-2.01)[1]
Stockwell, et al., 1992	USA	not presented (210/301 total)	female	exposure at work	"no statistically significant increase in risk"

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Wu, et al., 1985	USA	not presented (29/62 total)	female	exposed at work	1.3 (0.5-3.3)
Wu-Williams, et al., 1990	China	415/602	female	exposed at work	1.1 (0.9-1.6) 1.22 (0.95-1.57)[2] 1.1 (0.86-1.41)[1]

* statistically significant

1. LeVois, M.E., and Layard, M.W., "Controversy Over Regulating Indoor Air Quality: Environmental Tobacco Smoke," comment submitted to U.S. Occupational Safety and Health Administration, Docket H-122, No. 3-1067, March 19, 1992.

2. Lee, P.N., Environmental Tobacco Smoke and Mortality. Basel, Karger, 1992.

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was presented, that is, the one for the most extreme self-reported exposure category, was also not statistically significant.

Another U.S. study is the 1988 Ph.D. dissertation of Butler. (Ex. 8-47) This cohort study followed two groups of California Seventh-Day Adventists, members of a religious sect who adhere to certain lifestyle choices, e.g., abstinence from smoking, caffeine and red meat. Despite the lifestyle differences suggested by membership in this sect, Butler's data have been included in discussions of workplace ETS exposure. For males, Butler reported a risk estimate of 1.72 (95% CI 0.33-9.04); for females, the reported risk estimate was 1.47 (95% CI 0.15-14.06), for having worked with a smoker for eleven or more years. Neither was statistically significant. Despite the large number of individuals enrolled in the study, very few lung cancer cases were obtained. As a result, an extremely small sample size is a major flaw in this study.

Another American study was first published in 1991 by Fontham and colleagues. (Ex. 8-106) It represented a preliminary report on a case-control study of women in five U.S. cities, and is extensively relied upon in the OSHA Notice. For all lung cancer cell types combined, an odds ratio of 1.34 (95% CI 1.03-1.73) was reported for those women who reported that they were ever exposed to ETS in an occupational setting. Fontham and colleagues (1994)

have recently published a report on all five years of the study.[11] They present a "crude" risk estimate for workplace exposure of 1.12 (95% CI 0.91-1.36), which changes dramatically after adjustment for a number of variables to 1.39 (95% CI 1.11-1.74). The magnitude of the change following adjustment is much more pronounced for the workplace risk estimate than for the other risk estimates in the paper. Moreover, the upward increase after adjustment is suspicious. Fontham and colleagues do not address this apparent discrepancy. Because of OSHA's reliance on the 1991 Fontham, et al., study, it is presumed that the second study will be used by OSHA as the rulemaking proceeds. Therefore, a more detailed discussion of the Fontham study will be found in the discussion of OSHA's "risk assessment" in this submission.

Another U.S. study, by Garfinkel and colleagues, was a case-control study of hospitalized women in New Jersey and Ohio, published in 1985. (Ex. 8-119) It included the following estimation of workplace exposure to ETS:

> The interviewer also asked about the average number of hours a day the woman had been exposed to the smoke of others at any time during the past five years, during the past 25 years at home, while at work . . .

The authors reported the following:

> [The] OR for exposure at work during the last five years was 0.88 [95% CI 0.66-1.18; 14 cases, 52 controls]; for the last 25 years, it was 0.93 [95% CI 0.73-1.18; 34 cases, 118 controls].

These two point estimates represent negative associations between reported ETS exposures in the workplace and lung cancer in nonsmokers.

Conclusions based on a case-control study of 191 men and women in New York State were reported in 1990 by Janerich and colleagues (Ex. 8-164), who wrote:

> Exposure in the workplace was measured by recording the number of smokers who worked with each study subject during his or her lifetime and the amount of time the subjects spent working with these smokers. These exposures were compared for case patients and control subjects. Estimating the odds ratio as a continuous variable for an equivalent differential of 150 person-years of exposure gave an odds ratio of 0.91 (95 percent confidence interval, 0.80 to 1.04), indicating <u>no evidence of adverse effect of environmental tobacco smoke in the workplace</u>. [emphasis added]

In 1984, Kabat and Wynder published results of a case-control study of hospitalized individuals, mostly from New York City. (Ex. 8-171) A total of 25 male cases and 53 female cases and their matched controls were included. The authors wrote:

> The plausibility of a role of passive inhalation in lung cancer can be questioned on several grounds . . .
>
> Cases do not differ from controls except for the greater exposure to cigarette smoke at work reported by male cases compared to male controls.

The authors reported that 18 of 25 male cases versus 11 of 25 controls reported being exposed to ETS in the workplace. This result was statistically significant at P = 0.05. The point estimate for workplace exposure of males was reported elsewhere as 3.27 (95% CI 1.01-10.6). However, the authors' reported results for women are inconsistent with their conclusions on men; 26 of 53 female cases versus 31 of 53 controls (i.e., fewer cases than controls) reported exposure in the workplace. This result, a point estimate of 0.68 (95% CI 0.32-1.47), is not statistically significant.

In 1990, Kabat reported preliminary results from an American Health Foundation case-control study, which then included 90 cases and 247 controls.[7] Kabat reported that "preliminary analyses of the data do not indicate any striking ETS exposure differences between cases and controls." Specifically, he reported odds ratios for men of 0.98 (95% CI 0.46-2.10) and for women of 1.00 (0.49-2.06), for reported workplace exposure. The risk

estimate for males is negative, and that for females is the same as the baseline, "no-risk" level.

One of the European case-control studies to assess workplace exposure was conducted on hospitalized women in Athens, Greece.[8] Based on 89 cases and 118 controls, the authors conclude: "The effect of exposure to passive smoking at work was very small and not statistically significant (the RR between extreme quartiles was 1.08 (0.24-4.87))."

Koo and colleagues, in their 1987 case-control study of women in Hong Kong, included an assessment of workplace exposure in an accounting of total lifetime exposure to ETS. (Ex. 8-183) The authors concluded:

> On the basis of our extensive life-history data, we were able to calculate the total years, hours, mean hours/day, and cigarettes/day to which the subjects had been exposed to tobacco smoke at home or at work.
>
> Despite such detailed accounting, we were unable to find a significant trend in the crude or adjusted RR for these 4 lifetime measurements of passive smoking.

In a 1984 publication, Koo and colleagues reported a risk estimate for women exposed at the workplace of 0.91; this negative association was reportedly not statistically significant.[10]

Another European study including an assessment of ETS exposure in the workplace and nonsmoker lung cancer was published in 1986 (Ex. 8-192). The authors wrote that "overall the results showed no evidence of an effect of passive smoking on lung cancer incidence among lifelong nonsmokers," although they presented no odds ratios for workplace exposure. The following point estimates have been presented by one of the authors of this study in a recent book: for females, 0.63 (95% CI 0.17-2.33) and for males, 1.61 (95% CI 0.39-6.60).[12]

Shimizu, et al., reported that, in their case-control study of 90 women in Nagoya, Japan (Ex. 8-283):

> Passive smoke exposure at work was not clearly associated with female lung cancer, although the relative risk was slightly elevated (RR = 1.2).

That reported relative risk was not statistically significant.

In 1992, Stockwell and colleagues published data from a case-control study of nonsmoking women in Florida. (Ex. 8-292) The authors wrote: "We found no statistically significant increase in risk associated with exposure to environmental tobacco smoke at work." However, they failed to present the data associated with this index of exposure.

In 1985, Wu and colleagues reported on a case-control study of women in a Los Angeles, California tumor registry. (Ex. 8-326) For adenocarcinoma, the authors wrote, "we did not observe any elevated risk associated with passive smoke exposure . . . at work (RR = 1.3; 95% CI = 0.5-3.3)."

A joint Chinese-American study of women in Shenyang and Harbin, two industrial cities in northeast China, reported that 228 cases and 301 controls had been exposed to ETS in the workplace.[9] A relative risk of 1.1 (95% CI 0.9-1.6) was calculated, which the authors described as a "small excess risk," although it was not statistically significant. The authors also noted that "there were no significant dose-response trends associated with years of passive smoke exposure at work."

While the same criticisms that apply to the spousal smoking risk estimates apply to the workplace risk estimates (no actual measurements of exposure, failure to account for sources of bias and for potential confounding factors, poor study design, weak reported associations), the workplace data are, nevertheless, most appropriate for OSHA's purpose.

As illustrated in Table 1, only two of the reported risk estimates are statistically significant. The overwhelming majority, 16 of 18 risk estimates, are not statistically

significant. **Taken as a whole, these data do not support the existence of an association between workplace exposure to ETS and lung cancer risk in nonsmokers.**

> **Analyses of the workplace data as a whole, which were not considered by OSHA, do not support the claim of an increased risk of lung cancer due to ETS exposure in the workplace**

As EPA did in its Risk Assessment on ETS, to justify extrapolating from spousal smoking to other exposures, OSHA makes the claim at 59 FR 15994 that:

> [H]ealth effects observed and the risk estimates calculated from studies of the general population, or of selected subgroups, such as nonsmoking wives of smoking husbands, are relevant to the working nonsmoking population.

OSHA continues:

> [R]isk estimates based on residential exposures are expected to accurately reflect occupational risks in most workplaces and possibly underestimate the risk in some workplaces.

By neglecting the data on ETS exposures in the workplace available in the studies of spousal smoking and lung cancer, OSHA

overlooks a serious inconsistency in these data, as did EPA. As recently noted by LeVois and Layard:[13]

> The EPA's fourth point, that ETS exposure in workplaces is comparable to home exposure, and therefore if home exposure can cause lung cancer, so can workplace exposure, is not an argument for dismissing the workplace epidemiology at all. Rather, it simply avoids the question of why, if domestic and workplace exposures are comparable, the combined workplace data do not indicate any ETS-lung cancer association.

LeVois and Layard conclude:

> The fact that workplace studies produce a risk estimate that disagrees with the estimate derived from aggregated spousal smoking studies cannot be dismissed by making speculative assumptions about study design validity. . . . The workplace ETS study design avoids problems of spousal concordance with respect to lung cancer risk factors and introduces fewer potential biases and confounders than are present in the spousal study design. Thus, workplace ETS-lung cancer data are probably <u>less</u> flawed than are the spousal smoking data. [authors' emphasis]

OSHA should utilize all the available data on workplace ETS exposures from the epidemiologic studies on ETS and lung cancer

In its Notice, OSHA arbitrarily chose the workplace smoking risk estimate from the Fontham, et al., (1991) study to use in its calculation of risk. (Ex. 8-106) As detailed above, the reported result of Fontham, et al., both in the 1991 report and the 1994 report, is one of only two statistically significant risk estimates for workplace exposure. OSHA fails to address what would have happened to its calculations of risk if the risk estimate from another of the workplace studies, such as that of Janerich, et al., were used instead.

Moreover, the statistical technique of meta-analysis, although of somewhat questionable applicability to the analysis of epidemiologic studies such as these,[14] has been applied to the workplace data. Recent meta-analyses generated summary risk estimates, based on those studies then available, of 1.01 (95% CI 0.92-1.11)[13] and 0.98 (95% CI 0.89-1.08).[12] These risk estimates are not statistically distinguishable from 1.0, the "no effect" level in epidemiology. Although meta-analysis has its limitations, it does provide one means of assessing <u>all</u> the available data.

<u>OSHA's calculation of attributable risk is based on a single, arbitrarily selected risk estimate; it would seem to be highly sensitive to changes in the values of the variables used; OSHA fails to discuss the uncertainty of this estimate</u>

At Section IV.D. (59 FR 15995), the choice of the risk estimate from the Fontham, et al., 1991 study (Ex. 8-106), which OSHA attempts to justify on the basis of the quality of the study (without discussing published criticisms of Fontham, et al.[15,16]), nevertheless seems arbitrary, given the amount of additional workplace data available. OSHA arbitrarily ignores 13 other studies that give workplace risk estimates, and arbitrarily switches from reliance on the spousal smoking data in the rest of its text, to a workplace estimate for the attributable risk calculations.

<u>The Fontham, et al., 1994 study, though based on a large sample of nonsmoking women, may be criticized for a number of shortcomings</u>

If OSHA, as anticipated, relies on data from the second report on the Fontham study[11] to replace the data from the interim report cited in the Proposed Rule, it is submitted that OSHA should do so carefully. The makeup of this study population is likely quite dissimilar to the United States workforce as a whole. OSHA has available data from 14 worldwide workplace studies or nine

United States workplace studies, including data on both men and women. Rather than arbitrarily choosing one study, which, despite its claimed methodological advances, still does not resolve the issues of accurate exposure assessment or misclassification of smokers as nonsmokers, OSHA should consider all the available data on <u>workplace</u> exposures to ETS.

The following comments address the 1994 Fontham, et al., report:

- Despite the study's use of cotinine to assess current tobacco use, the authors acknowledge that misclassification of ever smokers as <u>lifetime</u> never smokers is "problematic" because there is "no biomarker of lifetime tobacco use." Moreover, only slightly more than half (54%) of cases had cotinine determinations. Thus, not even <u>recent</u> active smoking was excluded for nearly half of the cases.

- While the authors stress that their study is a <u>multicenter</u> case-control study, if the characteristics of the study population are examined, it is seen that the vast majority of cases and controls come from two areas in California (Los Angeles and the San Francisco Bay area). Yet, the authors do not indicate that air pollution, which has been suggested to be a lung cancer risk factor,[17] was "adjusted" for in their

analyses. In fact, the authors provide no breakdown of the data by study center, and it is not possible to ascertain whether the reported risks were consistent across the centers. Heterogeneity in the data among study sites would argue against combining the data as was done in this paper.

- Among other potential confounders that were not considered in the analyses is dietary saturated fat intake, recently reported by Alavanja, et al., to be associated with relative risks as high as 6.0 to 11.0.[18] The risk was highest in nonsmoking women with adenocarcinoma; over 75% of the cases in the Fontham, et al., study were adenocarcinomas. Alcohol consumption, another potential confounder, was also not mentioned. Recent studies have reported that smokers, and the persons living in their households, are likely to consume more fatty foods and more alcohol.[19,20]

- The presentation in the Fontham, et al., study does not provide data for the possible associations between diet and other potential confounders and lung cancer. It is thus impossible to judge whether fruit and vegetable consumption was associated with lung cancer risk but not with smoking status, or with smoking status but not with lung cancer risk. The reader must take the authors' position that the factors

were not confounders at face value, without the opportunity to examine the data.

- The "adjustment" of the reported risk estimates is difficult to interpret, as the adjustments take into account both study design variables (e.g., subject age) and potential confounders. It is not possible to determine what might be affecting the adjustment. In particular, the dramatic upward shift (1.12 to 1.39) in the risk estimate for workplace exposure is puzzling and surprising. The shift is opposite the direction expected, and is of a magnitude unlike the other adjustments in the paper.

- The study population characteristics also reveal that over 70% of cases and controls were aged 60 or older. This calls into question the accuracy of childhood exposure estimates provided by these women, who were asked to recall parental smoking habits of more than 50 years ago.

- Furthermore, the socioeconomic and educational composition of the study population argues against generalizing results reported from this study to the United States population as a whole. The majority of cases and controls were drawn from low socioeconomic strata: more than 40% had <u>household</u> incomes of

less than $20,000. In terms of education, one-third of cases had no more than a high school education.

- The conclusion stated in the abstract of the paper -- "Exposure to ETS during adult life increases risk of lung cancer in lifetime nonsmokers" -- gives the appearance that the reported results are applicable to both men and women, when in fact, only women were studied.

- Fontham and colleagues neglect to discuss the available workplace data from other spousal smoking studies. Of particular interest is the note that several large recent case-control studies (Janerich, et al.; Brownson, et al.; Stockwell, et al.; Wu-Williams, et al.) have reported results for workplace exposure that were <u>not</u> statistically significant. Fontham, et al., should have put their data in context.

OSHA FAILS TO REFERENCE THE NUMEROUS CRITICISMS THAT HAVE BEEN MADE CONCERNING THE EPIDEMIOLOGIC STUDIES OF REPORTED ETS EXPOSURE AND LUNG CANCER

At 59 FR 15980, OSHA writes:

> The great number of epidemiologic studies available on ETS were conducted by different researchers, on different populations, in various countries with diverse study designs. This extensive amount of data increases confidence that the associations seen between ETS exposure and the development of lung cancer is [sic] internally consistent and is [sic] not due to artifacts or a product of some unidentified, indirect factors unlikely to be common to all of the studies.

OSHA fails to reference these claims.

OSHA does not address the issue that actual ETS exposures were not measured in any of these studies reporting data on workplace exposure or spousal smoking. These studies relied upon questionnaires to provide an estimate of exposure, usually presented as the smoking habit of the cases' husbands. Concerns about the reliability of questionnaires used in ETS studies have been raised in the scientific literature.[21-23] (See also discussion of ETS exposure studies elsewhere in this submission.)

Based on the text of the Proposed Rule, OSHA does not appear to be aware that members of the scientific community have criticized the epidemiologic studies on ETS exposure and lung cancer for failing to consider certain factors, namely bias and confounding, that could affect the validity of the studies' risk estimates. The impact of such factors is particularly important in studies that, like these studies, report risk estimates that are "weak."[24] A weak association is represented by a risk estimate of less than 2.0 or perhaps even less than 3.0.[25-27] As Wynder notes[25]:

> [E]pidemiology has problems when the associations are of a low order of magnitude. In such instances, findings in the literature are, in general, inconsistent. . . .
>
> When risks are small, and especially when effects occur many years after their causes, detecting them, estimating their magnitude, and assessing their importance for the community in light of other relevant factors pose problems of study design, data collection, analysis, and interpretation which can be exceedingly difficult. (p. 139)

A detailed discussion of criticisms relevant to evaluation of the spousal smoking studies may be found in the Philip Morris submission to OSHA's Request for Information on Indoor Air. (Ex. 3-1074, Question 2(a)iii) Other submissions discussing the limitations of these studies include Exs. 3-331 and 3-1195. Additional recent articles are appended with this submission (e.g., Layard, 1992; Katzenstein, 1993).[28,29]

In the Proposed Rule, OSHA simply writes, without referencing its contentions, that:

> Many potential sources of bias, such as publication bias (the tendency of scientific journals to publish studies with positive results), misclassification bias (smokers or former smokers claiming to be nonsmokers), and recall bias (the reliance on self-reporting of personal smoking habits and exposure to others' tobacco smoke) can not account for the elevation in risks seen in these various studies.

OSHA must explain how it arrived at this conclusion, given the published literature suggesting that such sources of bias may indeed account for the reported elevations in risk. (See Ex. 3-1074) As but one example of a reference contrary to OSHA's claims, Lee has reported that a realistic smoking status misclassification rate of less than 3% is sufficient to explain the risk estimates calculated in the U.S. spousal smoking studies.[12] If OSHA has analyzed the literature on bias, such an analysis should be presented.

OSHA, like EPA, has the erroneous impression that a single confounder must necessarily apply to all the studies in order for it to be important

Despite OSHA's claim to the contrary, the very diversity of the spousal smoking studies makes it exceptionally difficult to compare them in any meaningful way. It is not logical, given this diversity, to expect that the same lifestyle variables would pertain to a population in China as to a population in Sweden or the United States. A confounder need not be common to all the studies.

In epidemiology, a confounding factor must meet one condition: it must be associated both with the exposure variable being investigated (here, spousal smoking), and with the endpoint under consideration (lung cancer). As noted in a recent review[30]:

> Because the relative risks or odds ratios for human diseases reported to be associated with ETS exposure are typically no larger than the risks for confounding lifestyle factors, epidemiological studies of the association between ETS exposure and chronic disease should be designed to maximize data quality and statistical power.
>
> The ETS and chronic disease epidemiology studies conducted to date have not adequately controlled for all of the known confounding variables.

Another 1992 review addressed the possibility that confounding factors may have a combined effect on estimations of lung cancer risk.[31]

> In the absence of calculations of lung cancer risk when multiple factors apply, one can only speculate on the combined effect on an individual who, for example, might have a family history of lung cancer (RR = 2-4), lived in an urban area (RR = 1.2-2.8), worked in an occupation associated with elevated lung cancer risk (RR = 2 or more), was among the physically less active groups of the population (RR = 2) and, if a female, had the risk associated with a short menstrual cycle (RR = 2.2).

While these factors may not truly be confounders (that is, associated both with spousal smoking <u>and</u> with lung cancer), but instead, independent lung cancer risk factors (associated with lung cancer but <u>not</u> with spousal smoking), their potential contributions to lung cancer risk have not been adequately assessed in the spousal smoking studies.

A detailed discussion of confounders is presented in Philip Morris' submission to the docket on OSHA's Request for Information. (Ex. 3-1074; Response to Question 2(a)iii)

Since the time that submission was prepared, new studies have been published that provide additional relevant data on potential confounders of the claimed ETS-lung cancer relationship,

in particular, the possible effects of diet.[18-20,32-34] Some of these are briefly reviewed below.

Recent studies indicate that the diet of nonsmokers is related to the presence or absence of smokers in the household. The studies report that nonsmokers who live in smoking households "have a diet more like smokers," consisting of more fried and fatty foods, more alcohol, and less fresh fruits and vegetables. Some authors suggest that differences in lifestyle, such as diet, may influence differences in disease risk reported when smoking and nonsmoking households are compared.

For instance, a 1992 British study examined the consumption of fried foods, fats, fruits, vegetables, and sweets in smokers, nonsmokers, and exsmokers.[19] The authors reported that nonsmokers who live in smoking households "have a diet more like smokers," and that "diet could be an important confound in epidemiological studies of ETS." The authors also noted:

> Our analysis showed that non-smokers in smoking households ate fried food more often, more chips [french fries], less fruit in winter, more butter and less margarine high in polyunsaturates than non-smokers in non-smoking households. As we have pointed out, these habits are thought to increase the probability of cancer.
>
> These results suggest that it is wise to show caution when interpreting the disease patterns

of non-smokers in smoking households. Studies to date have failed to take into account the effect that differences in dietary and lifestyle behaviour between 'smoking' households and 'non-smoking' households may have on the incidence of cancer or heart disease.

In a 1993 paper, the same authors reported that, in addition to having higher intakes of saturated fats, never smokers living in smoking households consumed fats more often, drank more alcohol, and ate fewer root vegetables and cereal than did never smokers living in nonsmoking households.[20]

A large study conducted in the U.S. recently reported that nonsmoking women who consumed large amounts of saturated fat (i.e., a kind of fat found in meats, butter, and lard) had strongly elevated risks for lung cancer.[18] Although the authors did not compare their data on fat intake to household smoking status, they did note that "passive smoking did not affect risk estimates" in their study. The risk of lung cancer among nonsmokers who reported high consumption of saturated fats was almost three times higher than any overall risk estimate reported in the 35 spousal smoking studies. Indeed, the risks reported in the study for <u>lower</u> levels of estimated saturated fat consumption are comparable to any of the overall risk estimates reported in the studies on spousal smoking.

Another recent U.S. study reported that higher intake of raw fruits and vegetables, vitamin E supplements, and dietary beta carotene (a precursor of vitamin A) is associated with a statistically significant reduction in nonsmoker lung cancer risk.[32] If, as other data suggest, smokers and the persons who live with them are likely to consume less of these food items, then those individuals might have an increased risk of lung cancer. Whole milk intake was also greater among lung cancer cases in this study, which the authors suggested possibly "reflects an effect of dietary fat."

OSHA'S TREATMENT OF THE SPOUSAL SMOKING DATA IS NOT ONLY INAPPROPRIATE, BUT INACCURATE AND INCOMPLETE

Regardless of the fact that OSHA's reliance on the spousal smoking data in much of the Proposed Rule is inappropriate, OSHA should be aware that it's treatment of the spousal smoking data is nonetheless inaccurate and incomplete. Inclusion of all available spousal smoking studies is important because these very studies contain the workplace data relevant to OSHA's jurisdiction.

<u>OSHA's list of spousal smoking studies is incomplete and inaccurate; OSHA has failed to consider all available data</u>

In addition to the 27 spousal smoking studies referenced by OSHA (Exs. 8-4; 8-35; 8-36; 8-38; 8-47; 8-52; 8-65; 8-106; 8-117; 8-118; 8-119; 8-121; 8-122 and 8-148; 8-142 and 8-143; 8-153; 8-158; 8-164; 8-171; 8-183; 8-187; 8-192; 8-283; 8-286; 8-292; 8-296; 8-300; 8-326), there are a number of spousal smoking studies that were <u>not</u> included in OSHA's Proposed Rule.[7-9,35-39] Copies of those studies published as of early 1992 were provided to OSHA in Philip Morris' submission on the OSHA Request for Information on Indoor Air (Ex. 3-1074; response to Question 2(a)iii).

One of the studies that OSHA failed to consider, Wu-Williams, et al., was conducted in China and is one of the largest case-control studies on this issue published to date.[9] Wu-Williams and colleagues report, for spousal smoking, a <u>statistically significantly negative</u> risk estimate. Another of these studies, Kabat (1990), is a preliminary report on a United States case-control study.[7] That initial report, which presented <u>no</u> statistically significant risk estimates, suggests that this study is controlling for a number of potential study design problems.

OSHA's citations of lung cancer studies at 59 FR 15980 are inconsistent when compared to the studies cited in Table IV-1.

(59 FR 15993) For instance, OSHA cites the important 1981 cohort study by Garfinkel (Ex. 8-118) at 59 FR 15980, but fails to include it in Table IV-1. (59 FR 15993) OSHA also cites a letter to the editor (Ex. 8-252) as one of the ETS-lung cancer epidemiologic studies (59 FR 15980), yet fails to reference the actual study.[39] A study by Kalandidi, et al., is included in Table IV-1, but is not referenced in OSHA's Exhibit 8.[8]

OSHA also "double-cites" at least one study, by treating Gillis, et al., (Ex. 8-122) and Hole, et al. (Ex. 8-148) as unique studies. These two papers are both reports from the same Scottish cohort study. By treating them as two separate studies, OSHA essentially counts the data twice.

Two of the papers cited by OSHA have been rejected in other reviews of the literature on ETS and lung cancer. The reasons for those rejections are described below.

- Katada, et al., 1988 (Ex. 8-175): The reference categories (i.e., nonexposed women) are too small to allow appropriate calculations of relative risk (because all of the cases reported ETS exposure). The U.S. EPA did not use the study in any of its analyses. (Ex. 8-311)

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- Sandler, et al., 1985 (Exs. 8-275 and 8-276): The methodology and interpretation of this study has been criticized in the scientific literature (e.g., one scientist described Sandler's work as "seriously flawed").[40a-f] The data presented are of limited value, for instance, the lung cancer estimates are based on only two cases. Neither the U.S. EPA (1992) (Ex. 8-311) nor the National Academy of Sciences (1986) (Ex. 8-239) included this study in their summary analyses of ETS issues.

OSHA's argument in support of the case-control studies on spousal smoking is flawed and reveals a lack of familiarity with the available literature

At 59 FR 15980, OSHA states:

> [T]he relative risks that were estimated from prospective study data are similar to those estimated from case/control [sic] study data. Biases that may be problematic in case-control studies are not a problem in prospective studies. Since the results from both types of studies are similar it is apparent that these biases are not important in the case-control studies (e.g., misclassification bias and recall bias). This information strengthens the confidence of a causal connection.

OSHA fails to provide references to support the contention that biases are not a problem in cohort studies, nor does OSHA provide

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references to justify its conclusion that biases are not operating in the case-control studies.

Misclassification of smoking status can certainly occur in a cohort study, just as in a case-control study.[41] For instance, a person may misreport his or her smoking status in the initial interview; personal smoking status may change over the course of the study; spousal smoking status may change over the course of the study. Follow-up in cohort studies must take these possibilities into account. Similarly, confounding factors associated with marriage to a smoker could operate in a cohort study as well as in a case-control study.

Moreover, while the cohort study may well be a preferred tool for epidemiologic research, OSHA has failed to recognize that the cohort studies on spousal smoking published to date have been criticized in the scientific literature. Of the four such studies available, two (Gillis/Hole, Exs. 8-122 and 8-148, and Butler, Ex. 8-47), have less than ten nonsmoker lung cancer cases each. These extremely small sample sizes reduce confidence in the risk estimates reported in those studies.

The other two studies, Hirayama (Exs. 8-142 and 8-143) and Garfinkel (Ex. 8-118), report data on larger numbers of nonsmoking women. The results of the two studies, however, are not

consistent, with Hirayama reporting a statistically significantly overall risk estimate, while Garfinkel reported no statistically significant overall risk for spousal smoking.

The Hirayama study has been heavily criticized in the scientific literature, for its mathematical errors, unconventional statistical methods, and inconsistencies in the data presented.[42-50] In particular, researchers have criticized Hirayama's techniques of age adjustment, an important consideration since age may act as a confounding factor in epidemiologic calculations.[44-49] It has been noted that Hirayama did not divide his study population into appropriate age groups, and that he also adjusted his analyses by husband's age, rather than by wife's age, contrary to common epidemiologic practice. Information available about the study also suggests that as few as 12% of the cases were histologically confirmed.[46] This means that bias could have been introduced if, among the 88% not confirmed, some died of causes other than lung cancer.

Thus, had OSHA critically examined the cohort studies of spousal smoking and lung cancer, and reviewed relevant literature critical of those studies, it would have seen that the cohort studies are not free of problems, contrary to its unsubstantiated claims.

OSHA fails to provide sufficient information to justify its classification of the spousal smoking studies in support of its quantitative risk assessment

At 59 FR 15992, OSHA states:

> As a first step in this risk assessment, OSHA critically reviewed epidemiologic studies associating exposure to ETS . . . with adverse health effects. The purpose of such a critical evaluation was to determine whether exposure to ETS is a causal factor in cancer . . . (59 FR 15992)

However, OSHA fails to provide adequate information for the reader of the proposal to evaluate how OSHA conducted this "critical evaluation" or review.

As noted earlier, OSHA's evaluation focuses on the data on spousal smoking. These are not the best available data for OSHA's purpose, as other data exist on ETS exposures <u>in the workplace</u> and lung cancer risk. Nevertheless, OSHA's treatment of the spousal smoking studies in this section of the Proposed Rule deserves comment.

In its discussion, OSHA continues (59 FR 15992-15993):

> OSHA evaluated studies on exposure to ETS to determine the importance and weight of each study in the overall hazard identification process. Of those, it was determined that fourteen showed a statistically strong association between exposure to ETS and lung cancer . . . Studies that were determined to be positive by OSHA's review standards met standard epidemiologic and statistical criteria to support causation. (59 FR 15992-15993)

OSHA's Proposed Rule does not describe in sufficient detail the criteria used to determine that certain of the spousal smoking studies on lung cancer were "positive," "equivocal with a positive trend," and "equivocal." Although OSHA lists the studies according to these categories in Table IV-1 (59 FR 15993), that table <u>does not</u> include any numerical data. It is not possible to determine whether OSHA used a single risk estimate from the study (and if so, which one), or whether OSHA somehow evaluated all the data presented in each study. Without the criteria used by OSHA, the classification gives the appearance of being arbitrary and based on unknown subjective standards. OSHA should clearly present its criteria for judging studies to be "positive" or to show "a statistically strong association."

In particular, it is not clear how OSHA can make this statement given the lack of statistical significance in the spousal smoking studies (only six report statistically significant overall relative risks), and specifically, the statistically nonsignificant

overall risk estimates included among the 14 studies in OSHA Table IV-1 that are described as "positive for an association" (59 FR 15980), "positive" (59 FR 15993), or "statistically strong" (59 FR 15992). Of those 14 studies, less than half report statistically significant overall risk estimates.

If the overall risk estimates reported in these studies are examined according to the criteria of statistical significance and the magnitude of the reported risk estimates, a different classification emerges (Table 2). Of 35 currently available studies, 11 report overall risk estimates less than or equal to 1.0; one of these is statistically significantly negative. These risk estimates are compatible with the hypothesis that there is no increased risk associated with ETS exposure, reported as spousal smoking.

Furthermore, 17 of the studies report overall risk estimates ranging from 1.0 to slightly greater than 2.0, none of which is statistically significant. Therefore, all of these risk estimates are compatible with the hypothesis of no association.

Only seven studies report overall risk estimates that are statistically significant. **In summary, then, 28 of 35 spousal smoking studies (80%) report overall risk estimates that do not support a conclusion of increased risk.**

TABLE 2: RESPONSE TO OSHA TABLE IV-1, BREAKDOWN OF SPOUSAL SMOKING STUDIES

Risk Estimate ≤ 1.0 -- Not Statistically Significant	Risk Estimate ≥ 1.0 -- Not Statistically Significant	Risk Estimate > 1.0 -- Statistically Significant
Brownson, et al., 1992	Akiba, et al., 1986	Geng, et al., 1988
Buffler, et al., 1984	Brownson, et al., 1987	Hirayama, 1984
Chan and Fung, 1982	Butler, 1988	Kalandidi, et al., 1990
Gao, et al., 1987	Correa, et al., 1983	Lam, et al., 1987
Janerich, et al., 1990	Du, et al., 1993	Lam, 1985
Kabat, 1990	Garfinkel, 1981	Trichopoulos, et al., 1983
Kabat and Wynder, 1984	Garfinkel, et al., 1985	Fontham, et al., 1994
Lee, et al., 1986	Hole, et al., 1989	
Liu, et al., 1991	Humble, et al., 1987	
Sobue, et al., 1990	Inoue and Hirayama, 1988	
Wu-Williams, et al., 1990*	Koo, et al., 1987	
	Lan, et al., 1993	
	Pershagen, et al., 1987	
	Shimizu, et al., 1988	
	Stockwell, et al., 1992	
	Svensson, et al., 1989	
	Wu, et al., 1985	

* Statistically significantly negative

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It is particularly puzzling how OSHA can justify its description of the Brownson, et al., 1992 study's reported results as "positive" when that study reports an overall risk estimate of 1.0. According to epidemiologic convention, 1.0 is the "no-effect" level.

OSHA states at 59 FR 15993 that:

> Overall, on the basis of the studies reviewed, OSHA concludes that the relative risk of lung cancer in nonsmokers due to chronic exposure to ETS ranges between 1.20 and 1.50 . . .

OSHA provides the reader of the Proposed Rule with no support for this conclusion. (See subsequent discussion of meta-analysis.)

OSHA's choice of "summary analyses" is restricted to meta-analyses of spousal smoking data rather than the more appropriate workplace data

OSHA's Table IV-3 is titled "Published Risk Estimates for Lung Cancer." The numbers in the table are all summary risk estimates calculated by combining risk estimates from a number of epidemiologic studies, through a procedure called meta-analysis. This is not made clear in the Notice; in fact, only one of the risk estimates in the table is identified as based on "pooled studies."

(Ex. 8-311) Moreover, the summary risk estimates presented by OSHA are based on the spousal smoking data, rather than the data on workplace ETS exposures that have been published.

Setting aside the question of the appropriateness of using meta-analysis to combine data from epidemiologic studies,[21] if OSHA references meta-analyses, then its list should be accurate and complete. Table IV-3 is neither (e.g., a recent meta-analysis by Tweedie and Mengersen is excluded[51]).

For instance, OSHA fails to indicate the number of studies included in each meta-analysis, and whether the analyses are restricted to a certain set of studies. The meta-analyses are not completely comparable, as they incorporate different subsets of the universe of available studies. Moreover, a review of more recent meta-analyses reveals that the summary risk estimates are sensitive to the inclusion or exclusion of studies.

The example most illustrative of this is provided by the meta-analysis from the 1992 EPA Risk Assessment on ETS. (Ex. 8-311) EPA reported a summary risk estimate of 1.19 (90% CI 1.04-1.35) based on 11 spousal smoking studies conducted in the United States. In a recent paper, LeVois and Layard report[13]:

> Using the EPA's methods and assumptions, we have calculated a summary relative risk of 1.07 from a meta-analysis of 13 U.S. female spousal smoking studies, including these two recent studies [Brownson, et al., Ex. 8-36, and Stockwell, et al., Ex. 8-292]. This relative risk, with 95% confidence interval of 0.95-1.21, is not statistically significant.

Thus, the inclusion of two additional studies in the meta-analysis effectively reverses the conclusion of the EPA Risk Assessment on ETS. The summary relative risk is no longer statistically significant, and, therefore, does not support a conclusion of an association between spousal smoking and lung cancer.

OSHA'S CLAIM THAT ANIMAL INHALATION STUDIES SUPPORT THE "CARCINOGENICITY" OF ETS IS NOT SUPPORTED BY THE SCIENTIFIC LITERATURE

At 59 FR 15980, OSHA proposes: "Animal studies have shown the carcinogenicity of cigarette smoke." This assertion, which OSHA fails to reference, is directly in contrast to a recent review of the relevant literature by Rodgman, who cautions[1]:

> Classifying a substance as tumorigenic or 'carcinogenic' can be misleading. Often, these terms are overinterpreted. One must be aware of the precise meaning and limitations of the terms tumorigenicity and carcinogenicity when applied to specific compounds and must exercise considerable care in the use of these and related terms.
>
> * * *
>
> Many of these 43 MS and/or tobacco components [claimed to be carcinogens] should be excluded from the list on the basis of published data on their tumorigenicity (or lack of it) in laboratory animals at levels determined in MS, their lack of tumorigenicity in most instances on inhalation, and the equivocal evidence of their tumorigenicity in humans at levels in MS.

In this major review, Rodgman also writes:

> [I]nhalation studies from 1936 to date involving lifetime exposure of laboratory animals to whole cigarette MS have consistently failed to induce squamous cell carcinoma . . .

> The failure to produce in MS-exposed laboratory animals the tumor type reported to be associated with smoking in humans is important not only with regards to the biological properties of MS itself but also with respect to that of diluted MS delivered to the caged animals. . . .
>
> If, as Stewart and Herrold (1962) noted, these smoke-inhalation experiments more closely resembled passive smoke (or ETS) exposure than human exposure during actual smoking, then substantial evidence is available to demonstrate that exposure to 'passive smoke' (or ETS), more concentrated than that encountered in the human situation, is ineffective in induction of the tumor type supposedly associated with cigarette smoking in humans . . .

These conclusions severely undermine OSHA's contention, and make further discussion of the literature cited by OSHA of limited value. Nevertheless, OSHA's treatment of the animal studies is scientifically unacceptable; for that reason alone it deserves comment.

OSHA's discussion of animal studies suggests a failure to understand the literature, and misrepresents the conclusions of a number of papers

OSHA's discussion of experimental animal data in the Proposed Rule represents a selective, biased review of the data. The presentation of data on animal exposures is neither balanced nor accurate.

In addition to misstatements of studies' conclusions, and misrepresentations of studies' data, OSHA's discussion of animal studies is pervaded by the following errors: assuming that mainstream smoke, sidestream smoke, and ETS are equivalent enough to be used interchangeably; and failure to acknowledge the differences among subchronic and chronic inhalation experiments. Examples of the inaccuracies and misrepresentations found in this section follow.

OSHA introduces its discussion of the animal studies by saying:

> Currently, OSHA is aware of only a few experimental inhalation studies with sidestream smoke or ETS reported in the literature. A discussion of these studies follows. [emphases added]

However, OSHA's choice of studies to include shows that OSHA did not restrict its analysis to sidestream or ETS studies. For instance, the first two papers referenced deal with gas-phase smoke. Their inclusion implies that OSHA may have made the erroneous assumption that the gas phase of whole smoke is equivalent to sidestream smoke or ETS. If so, this is a distinct misconception; any type of tobacco smoke (mainstream, sidestream, or ETS) consists of both a gas and a particulate phase. If the authors of OSHA's Proposed Rule were not operating under this

misunderstanding, then they instead misrepresented the articles under discussion.

Also, OSHA claims that "data suggest that sidestream smoke may contain more carcinogenic activity per milligram of cigarette smoke condensate than does mainstream smoke," citing to Ex. 3-689D. The exhibit available to the public was not labeled in such a way that Part "D" could be identified. This made it difficult to assess the reference for OSHA's claim.

In discussing Otto and Elmenhorst's paper (Ex. 8-247), OSHA states that this research has "shown that there are carcinogenic constituents in the vapor phase of tobacco smoke." Contrary to OSHA's assertion, the authors write: "the conclusion seems justified that tumor-inducing factors must be in the particle-phase of the smoke" [emphasis added]. The authors also indicate, in the summary of the study, that their chronic exposure regimen "had no significant effect on the spontaneous tumor-rate." Thus, this study, even given OSHA's misrepresentation of its conclusions, in no way supports OSHA's claim that the "carcinogenicity" of tobacco smoke has been shown in animal experiments.

Leuchtenberger and Leuchtenberger (Ex. 8-197) used neither ETS nor sidestream smoke as a surrogate for ETS. According

to their paper, they used "whole fresh cigarette smoke" or "its gas phase alone." The Leuchtenberger article is not an chronic inhalation study of ETS or sidestream smoke, as implied in the preceding paragraph. The results cited by OSHA (pulmonary adenomas and adenocarcinomas in male mice) are but one aspect of the data reported in the study. The authors comment that those changes could be found in control animals at a later age and lower frequency. The authors note that "chronic inhalation of the gas phase of fresh cigarette smoke did not evoke bronchogenic carcinoma" [emphasis added]; they also indicate that no bronchogenic carcinomas were observed in mice exposed to whole fresh smoke. Thus, the data from this study do not support OSHA's position.

Harris, et al., (Ex. 8-135) is correctly acknowledged as a mainstream smoke study by OSHA. With regard to their reported results, the authors stated that "spontaneous" tumors appeared in their control animals during the course of their chronic study, and said that "it would no longer be accurate to refer to the inhaled smoke:air mixtures as the cause of these tumors but merely as eliciting a higher incidence." Thus, according to the authors themselves, this study's data do not support a determination that cigarette smoke causes lung cancer in experimental animals.

In Mohr and Reznik (Ex. 8-226), one of the references cited by OSHA to support the statement "Studies have also reported hyperplasia and metaplasia in the trachea and bronchi of mice exposed to cigarette smoke by the inhalation route," the variability of the results reported from smoke inhalation studies is discussed. More importantly, Mohr and Reznik write:

> [T]he majority of investigations in tobacco smoke research have been conducted by some form of inhalation technique. . . . Nevertheless, no researcher has succeeded as yet in producing a significant incidence of pulmonary tumors. (p. 347) [emphasis added]

Thus, in its selective treatment of these data, OSHA uses a lengthy review paper to support a single statement. However, OSHA fails to discuss the concluding statements made by the authors of that review. Arguably, the most important point in this review paper is what the authors noted above: that animal inhalation studies using tobacco smoke have not reported a significant increase in pulmonary tumors in exposed animals. This statement casts doubt over all of OSHA's contentions that animal inhalation experiments support the claimed carcinogenicity of ETS.

In the discussion of a paper by Davis, et al. (Ex. 8-79), which again deals with chronic exposure to vapor-phase smoke, not sidestream smoke or ETS, OSHA presents the data in such a way that

the paper's lack of a statistically significant result is effectively obscured. While OSHA's statement that: "Pulmonary squamous neoplasms were detected in female Wistar rats exposed to a 1:5 smoke-to-air mixture. . . ." is not actually incorrect, it implies that the tumors were found only in exposed animals.

If one reads the conclusion of the paper cited, the following statement is found:

> The results provide convincing evidence that, under the conditions of the experiment, exposure to VP did not increase the incidence of any kind of neoplasm at any body site. (p. 467) [emphasis added]

The authors also note that cellular changes in the respiratory tract were no more frequent in exposed rats than in control rats.

While OSHA does make an accurate statement (i.e., that neoplasms were produced), its failure to present the complete picture, namely, that neoplasms were reported no more frequently among exposed than unexposed animals, is deceptive and misleading. The data presented in this paper do not support claims that animal inhalation studies show carcinogenic effects of tobacco smoke inhalation.

Some of the papers cited by OSHA, in this section which focuses on lung cancer, present data on tumors of sites other than the lung. Studies of this sort provide limited information pertinent to the issue at hand, namely, lung cancer. For instance, Dalbey, et al. (Ex. 8-77), reported a large number of benign adenomas or nasal tumors in chronically-exposed rats. Similarly, Dontenwill (Ex. 8-88) actually commented on the "very rare appearance of lung carcinomas" in his chronic inhalation study of hamsters (only 1 case).

Bernfeld, et al. (Ex. 8-30) reported on laryngeal changes, not changes to the lungs or bronchi. Moreover, the authors indicated that responses to chronic smoke inhalation varied greatly between the two hamster strains tested. If, then, two strains of the same species can exhibit markedly different responses in an experiment, by combining strains and species in the discussion and not considering the unique biology of the different animals tested, OSHA displays a overly simplistic view of biology.

In the discussion of the Auerbach, et al. (Ex. 8-19) study, in which dogs smoked through a tracheostomy, that is, a tube inserted into a hole cut into the animal's trachea (windpipe), OSHA did not even note that the Auerbach study used the tracheostomy method, as opposed to the exposure chambers used in the majority of the other studies discussed. More importantly, OSHA did not

address the inappropriateness of this route of exposure to either active smoking or ETS.

The Mohr and Reznik review (Ex. 8-226), cited by OSHA and discussed here previously, contains the following statements about the use of the tracheostomy method:

> [M]ost importantly, smoking through a tracheostomy is a <u>highly artificial system</u> and bears <u>little resemblance to human experience</u>. This is particularly the case when it is remembered that the normal dilution of smoke air is not achieved by this technique, with the result that the concentration of smoke is much higher than if taken in through the mouth.
>
> The most positive results have been obtained by means of tracheostomies in dogs. However, once again <u>the extreme artificiality of this system prevents any real correlation of the obtained experimental results to humans</u>. (p. 347) [emphases added]

Mohr and Reznik are discussing the relevance of data obtained in tracheostomy data to <u>active</u> smoking in humans. The relevance of these data to OSHA's Proposed Rule is certainly questionable, particularly given the extreme dilution of ETS once it is in room air.

Studies such as Grimmer, et al. (Ex. 8-127), discuss direct pulmonary implantation, in which a beeswax solution, containing a substance to be tested (here, condensed particles and

semivolatiles from sidestream smoke), is injected into the animal's lungs. The relevance of this experimental route of exposure in comparison to inhalation exposure is unclear. Moreover, the authors of the paper fail to present analyses of the statistical significance of their reported results. It is thus not possible to evaluate whether the paper supports OSHA's claims.

Dagle, et al., (Ex. 8-75) and Stanton, et al., (Ex. 8-289) report on the injection of a pellet of beeswax containing cigarette smoke condensate into the lungs of rats. Theoretically, this pellet would approximate chronic exposure, as substances "leach" from the pellet over time. However, as the authors of Ex. 8-289 note: "A major disadvantage is the unnatural exposure of respiratory epithelium to the carcinogen." Also, both these studies report simply on the <u>development</u> of this technique for bioassays.

In the subchronic study of Coggins, et al. (Ex. 8-59), aged and diluted sidestream smoke was used as a surrogate for ETS. This substance may be a more appropriate approximation of ETS than are other forms of tobacco smoke. While OSHA provides a factual summary of the conclusions of this study, they fail to note that effects (hyperplasia and inflammation) were reported only in animals exposed to particle concentrations some 100 times higher than typical real-world concentrations. Coggins, et al. (Ex. 8-60)

also report the same minor, completely reversible histopathological changes. The changes did not progress over longer periods of exposure, and once again occurred only at particle concentrations some 100-fold higher than real-world levels.

In a 14-day inhalation study, one would not expect lung tumors to develop. Thus, the relevance of the work of Coggins, et al., to OSHA's discussion of cancer is limited. Nevertheless, Coggins, et al. show only minor, reversible cellular changes following intense exposure to a surrogate for ETS.

At 59 FR 15981, OSHA cites to a book by Wynder and Hoffmann (Ex. 8-327) (the citation is unclear, particularly with respect to page numbers, as it is not a chapter or even a definable section), discussing "skin-painting" studies in which tobacco tar condensates were applied to mouse skin. In the very book cited, the authors write:

> The bioassay[s] for tobacco products on mouse epidermis have not answered questions on the problem of respiratory carcinogenesis. (p. 145)

Thus, the relevance of mentioning skin-painting studies in this context is unclear.

Reif, et al. (Ex. 8-259) reports on a "case-control" study in which owners of dogs that had died of lung cancer were asked about the dogs' exposures to ETS. Risk estimates for the dogs' developing lung cancer were then calculated. The study's authors note:

> The current study suffers from some of the same limitations found in the studies done in humans, i.e., small sample sizes, imprecise risk estimates, and difficulties in measuring exposure. (p. 238)

The "risk estimates" reported in this study were not statistically significant. Thus, these data in no way support the claim of an association between ETS exposure and lung cancer risk.

Not only do the data cited by OSHA fail to support OSHA's claims, but they represent a troubling approach to science. OSHA's Proposed Rule should be accurate and balanced: the complete data should be presented fairly, whether or not they support OSHA's position. To the reader unfamiliar with OSHA's process, misrepresenting data gives the impression that OSHA is using those data to achieve a predetermined conclusion, or that the staff responsible for the Proposed Rule did not understand the material reviewed.

OSHA's discussion of animal studies omits certain references concerning inhalation studies

Despite the fact that data from subchronic animal inhalation studies are of minimal relevance to the question of whether animal data support claims of the "carcinogenicity" of ETS, OSHA nevertheless chose to include some subchronic studies in its discussion. However, OSHA omitted several studies, which, in the interest of completeness, are described below. None of the studies report data supporting any permanent changes following subchronic exposure of animals to sidestream smoke at levels exceeding those encountered in "real-life" situations.

Haley, et al., 1987a, 1987b

Preliminary reports on this American Health Foundation study, in which hamsters were exposed to mainstream or sidestream smoke 7 days/week for 18 months, are available;[52,53] apparently, however, no final report has been published. In those reports, the authors note that smoke-exposed animals were living longer than were sham or cage control animals. No additional information was presented.

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von Meyerinck, et al., 1989

Rats and hamsters of both sexes were exposed to sidestream smoke at a concentration of 4 mg/m^3 TPM and 25-30 ppm carbon monoxide for 10 hours/day, five days/week for 90 days.[54] The authors noted about their exposure system: "The levels in the exposure chamber were at least 1 and in some instances 2 orders of magnitude higher than reported for smoke-polluted rooms under real-life conditions." (Elsewhere, the authors described these conditions as "unrealistically high."[55]) One hundred animals of each species were exposed, 115 of each species were sham controls, and 100 of each species were room controls. The authors reported minor, completely reversible histopathological changes in the nasal cavity in rats only, and no alterations in any other part of the respiratory tract.

Teredesai and Pruehs, 1994

Male rats and male hamsters were nose-only exposed to fresh sidestream smoke (FSS) for seven hours/day, seven days/week for 90 days.[56] One group of 20 animals was exposed to FSS with a total particulate matter (TPM) concentration of 2 ug/L, one to FSS with TPM of 6 ug/L, and one served as a sham exposure group. Histopathological changes described as "slight" were reported in the nose and larynx of exposed rats, "mainly in the high FSS

concentration group." These changes were reversible following cessation of exposure. The authors noted that "[n]o smoke-exposure-related histopathological changes were observed in trachea and lungs."

Thus, these additional studies not referenced by OSHA fail to support claims that animal data support the purported carcinogenicity of ETS.

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SECTION VI

MATERIAL IMPAIRMENT: CARDIOVASCULAR DISEASE

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CARDIOVASCULAR DISEASE

Introduction

This submission is set forth in two parts. Part I provides a critical evaluation of the claims and literature cited by OSHA in its Proposed Rule on the issue of ETS exposure and cardiovascular effects. Part I concludes that OSHA has not provided an adequate scientific foundation for its position that ETS exposure in the workplace increases the risk of adverse cardiovascular effects. Of particular importance is that OSHA has not based its position on the best available evidence, namely those epidemiological studies that actually attempted to estimate workplace ETS exposure in relation to heart disease risk. The best available evidence does not support a claim that workplace ETS exposure is associated with an increase in heart disease risk.

Part II provides a compilation of literature which raises questions about whether ETS exposure is associated with adverse cardiovascular effects. Most of this literature, despite its importance and relevance, was not even cited by OSHA. The literature in Part II includes conclusions from several major reviews. It also includes reports on several specific areas discussed incompletely or inadequately in OSHA's comments on cardiovascular disease. These areas include discussions of the extremely low levels of ETS or of ETS constituents to which

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nonsmokers might be exposed, as well as reports discussing research suggesting that any measurable cardiovascular responses to ETS are minor.

Part I: Response to Specific OSHA Claims

<u>OSHA HAS NOT PROVIDED AN ADEQUATE SCIENTIFIC FOUNDATION FOR ITS POSITION THAT ETS EXPOSURE IN THE WORKPLACE INCREASES THE RISK OF ADVERSE CARDIOVASCULAR EFFECTS</u>

The major discussion of cardiovascular effects in OSHA's Proposed Rule is provided at Section II.C.4. (59 FR 15977) The following discussion relates primarily to that section, although other portions of the notice are addressed as well, when warranted by their relevance to cardiovascular disease claims.

OSHA argues that research indicates that ETS exposure has a variety of adverse cardiovascular effects, including both acute effects, relating especially to oxygen supply and demand, and chronic effects, such as atherosclerosis and increased risk for the development of and death from coronary heart disease.

OSHA does not provide adequate support for its claim that ETS in the workplace should be regulated because of an association between ETS exposure and adverse cardiovascular effects. Much of the supporting literature cited by OSHA deals with active smoking, not ETS. Other studies, even though they may deal with ETS, are so flawed and limited in scope that they do not provide a sound basis for cardiovascular disease claims. Perhaps most importantly,

actual workplace data on ETS and heart disease are scant. Such data as exist do not support an association between workplace ETS exposure and cardiovascular disease.

OSHA DOES NOT BASE ITS CONCLUSIONS CONCERNING WORKPLACE ETS EXPOSURE AND HEART DISEASE RISK ON THE BEST AVAILABLE EVIDENCE. BASED ON THE BEST AVAILABLE EVIDENCE, WORKPLACE ETS EXPOSURE HAS NOT BEEN ASSOCIATED WITH A STATISTICALLY SIGNIFICANT INCREASED RISK OF HEART DISEASE.

Since OSHA's proposed rulemaking relates to the workplace, the best available evidence it should consider on the issue of heart disease risk and ETS exposure is that based on the workplace, not on residential exposure or spousal smoking. Of the epidemiological studies cited by OSHA relating to ETS and heart disease, three studies provided data on workplace exposure. These are: Dobson, et al. (Ex. 8-85); Lee, et al. (Ex. 8-191); and Svendsen, et al. (Ex. 8-295). Each of those reports provided estimates of the relative risk for heart disease mortality associated with workplace ETS exposure. The studies were consistent in not reporting a relationship of workplace ETS exposure with heart disease. Therefore, based on the best available evidence, the literature does not support OSHA's claim that workplace ETS exposure is related to heart disease in nonsmokers.

The three workplace studies are discussed more fully below.

Dobson, et al. (1991)

Dobson, et al., was a case-control study of myocardial infarction and heart disease mortality, which included questionnaire data relating to coworker smoking as an estimate of workplace ETS exposure. Odds ratios, with 95% confidence intervals, for workplace ETS exposure were reported as follows: 0.95 (CI: 0.51-1.78) for men and 0.66 (CI: 0.17-2.62) for women. Based on these data, Dobson, et al. concluded that the "odds ratios for passive smoking at work did not suggest increased risk."

Lee, et al. (1986)

Lee, et al., reported a hospital-based case-control study in which, in addition to information on spousal smoking, ETS exposure was estimated by asking the subjects about the extent to which they were exposed to ETS in four situations: at home, at work, during daily travel and during leisure time. Using a numerical index which combined questionnaire responses on ETS exposure in each of these situations, Lee, et al., reported relative risks of 0.52 (for lower combined exposure) on 0.61 (for higher combined exposure). Lee, et al, did not provide confidence

intervals, but stated that none of these risks ratios were statistically significant.

Svendsen, et al. (1987)

This study, although it primarily used spousal smoking as the estimate of ETS exposure, also included a small amount of information regarding workplace ETS exposure, as estimated from questionnaire data relating to smoking by coworkers. Comparing nonsmokers whose coworkers smoked to nonsmokers whose coworkers did not smoke, the following relative risks, with 95% confidence intervals, were reported for heart disease. For coronary heart disease mortality, the relative risk reported was 2.6 (CI: 0.5-12.7) and for fatal or nonfatal coronary heart disease combined, the relative risk reported was 1.4 (CI: 0.8-2.5). The wide confidence intervals include 1.0 and are, therefore, not statistically significant.

In sum, the best available evidence does not support the claim that workplace ETS exposure is associated with an increased heart disease risk. None of the three epidemiological studies cited by OSHA that include workplace data on ETS exposure and heart disease report a statistically significant association. Moreover, the relative risks in two of these studies are less than 1.0 (relatively fewer deaths in the ETS exposed workers).

OSHA provides inadequate support for its claims about ETS exposure and thrombus formation

OSHA addresses the issue of thrombus formation in the Proposed Rule at Section II.C.4.(a). (59 FR 15977)

OSHA argues that ETS exposure is involved in the formation of blood clots. OSHA cites only two laboratory studies to support this claim. Both of these studies focused on platelet activity. In one of these, Burghuber, et al. (1986) (Ex. 8-40), examined platelet function in a group of only nine nonsmokers, following a single exposure to high levels of ETS. The relevance of this artificial, short-term laboratory procedure to actual workplace conditions is highly speculative. Furthermore, these authors acknowledged that their test for platelet function in the laboratory may have no relevance to how platelets act in real life. They stated: "However, as with other platelet function tests, we do not know if this **in vitro** procedure accurately reflects platelet function **in vivo.**" (p. 37) The authors further acknowledged that it was not known whether their research had implications for cardiovascular function in ETS-exposed nonsmokers. They stated: "Further investigation is needed to elucidate whether this finding is important with respect to a possible increased incidence of thromboembolic disease among non-smokers passively exposed to cigarette smoke." (p. 37)

In another laboratory study cited by OSHA on ETS exposure and platelet function, Davis, et al. (1989) (Ex. 8-80), reported that 20 minutes of exposure to ETS increased platelet aggregation and also increased the number of endothelial cell carcasses in the blood. However, this was a highly limited study of only 10 male subjects, for which there was no true control condition. More specifically, in their exposure condition, the nonsmokers sat for 20 minutes in a hospital corridor where patients typically smoked. Not only does this constitute an imprecise ETS exposure, but it is not comparable to the control nonexposure condition. In the nonexposure condition, the nonsmokers sat in a laboratory where smoking was not allowed. A hospital corridor and a hospital laboratory are entirely different environments, involving potential confounding factors such as social conditions, noise factors, ventilation factors and a variety of other differences.

Other than the two laboratory studies, the only other citation with ETS data cited by OSHA was a 1991 report by Dobson, et al. (Ex. 8-85) This epidemiological study, in addition to reporting odds ratios for ETS exposure and heart disease, also provided data on fibrinogen concentrations. However, Dobson, et al. repeatedly noted that there was <u>no</u> statistically significant association of fibrinogen concentration with ETS exposure. Moreover, limitations of this study were explicitly acknowledged by the authors, thus making this paper unreliable as a basis for

OSHA's claims. For example, Dobson, et al. noted that there were "[d]ifferences in the methods of data collection and truthfulness in reporting smoking habits" between their exposed and nonexposed groups and that this might "have lead to bias." (p. 796) The potential effects of confounding factors, especially socioeconomic status, were noted, as well as the lack of statistical power in their study. In general, with regard to their epidemiological procedure, which was the basis for both the odds ratio and fibrinogen data, Dobson, et al. stated: "On balance, the effects of bias and confounding could have lead to overestimation of risks due to passive and active smoking." (p. 796)

Other citations listed in OSHA's review of the thrombus formation issue are not relevant to ETS. Some merely provide background or theoretical information concerning cardiovascular disease processes. (e.g., Exs. 8-111, 8-272) Others are studies of active smoking, not ETS. (Exs. 8-157, 8-224)

OSHA fails to adequately support its claim that ETS exposure is associated with vascular wall injury

OSHA addresses the issue of vascular wall injury in the Proposed Rule at Section II.C.4.(b). (59 FR 15977)

OSHA argues that ETS exposure may harm the endothelial lining of the arterial wall, but provides almost no support for this claim. In connection with this claim, OSHA refers to only one citation -- namely, the Davis, et al. (1989) report (Ex. 8-80), which, as noted in the previous section regarding thrombus formation, is a highly limited and flawed study.

OSHA's discussion of possible mechanisms of effect is not adequately supported; some of the cited references are irrelevant to this issue

OSHA addresses the issue of possible mechanisms of effect primarily in the Proposed Rule at Section II.C.4.(c). (59 FR 15977) Part of OSHA's discussion of risk assessment in Section IV.F.2, which addresses cardiovascular effects in relation to pharmacokinetic modeling, is also germane.

In Section II.C.4.(c), OSHA argues that there are three mechanisms by which ETS exposure "may place stress on the heart." The first mechanism is by decreasing myocardial oxygen supply. The primary manner in which ETS exposure theoretically might have this effect, as discussed by OSHA, is via formation of carboxyhemoglobin. OSHA cites only one study on this issue which actually involved ETS. This was a 1978 report by Aronow. (Ex. 8-13) The Aronow study is widely regarded in the scientific literature as being methodologically weak and unsubstantiated.

Furthermore, it is important to note that Aronow has been criticized severely for unethical and dishonest scientific practices, to the extent that the government no longer relies on his data. (Shephard, R., The Risks of Passive Smoking, London, Croom Helm Ltd., 73, 1982.) (Mintz, M., "FDA, Citing Phony Evidence, Bars Drug Tests by Researcher," The Washington Post, March 23, 1983.) (Peterson, C., "EPA Probe Criticizes a Study Used in Air-Quality Standard," The Washington Post, June 7, 1983.)

Although OSHA cites several additional reports in the context of discussing oxygen supply and demand (Exs. 8-242, 8-323, 8-324), these are reports on cigarette smokers, not of nonsmokers exposed to ETS.

The second mechanism for placing "stress on the heart" mentioned by OSHA is that oxygen demand may be increased via nicotine. However, OSHA does not provide any citations demonstrating that there is an association of ETS exposure with myocardial oxygen demand, much less an association with an increased demand specifically as a result of nicotine in ETS. Perhaps there is a theoretical argument, based on claims that nicotine is a pharmacological stimulant, for speculating that ETS may be associated with increased oxygen demand. Such an argument, however, does not recognize that the amounts of nicotine in ETS are extremely small and of doubtful physiological or cardiovascular

relevance. [See Part II.B. of this submission for examples of literature, ignored or not adequately addressed by OSHA, which relates to the minute levels of ETS, and of ETS constituents, to which nonsmokers might be exposed, and the doubtful cardiovascular significance of such exposure levels.]

The third mechanism discussed by OSHA is that ETS exposure may influence the cellular ability of the heart to utilize oxygen for energy production. The only citation on this point provided by OSHA is Ex. 8-123, which OSHA describes as a study demonstrating that healthy subjects became fatigued quicker when exercising in the presence of ETS. However, OSHA's description of Ex. 8-123 is incorrect. Ex. 8-123 is not a study of exercise performance and ETS. It is not even a research report with original data. It is merely a draft of a review paper by Stanton Glantz and William Parmley. In one section of their draft manuscript, Glantz and Parmley discuss an exercise study involving healthy subjects and ETS. This 1985 study by McMurray, et al. is elsewhere referenced by OSHA as Ex. 8-217. However, the McMurray, et al. report does not provide direct measurements of cellular oxygen utilization. Thus, it does not bear importantly on the issue for which OSHA cited it.

An additional heart disease mechanism proposed to be related to ETS is suggested by OSHA in Section IV.F.2., where

cardiovascular physiology is discussed in the context of pharmacokinetic modeling of ETS exposure. In Section IV.F.2., in addition to carbon monoxide and nicotine, OSHA proposes that polycyclic aromatic hydrocarbons (PAHs) have been associated with cardiovascular effects. To support this claim, OSHA cites the draft manuscript by Glantz and Parmley (Ex. 8-123), which presents no original data. It references several reports primarily dealing with injections of massive amounts of PAHs into chickens and pigeons. Given the doses and manner of administration, it is highly questionable whether this type of study has implications for any sort of inhalation exposure related to tobacco smoke, whether active smoking or ETS exposure.

OSHA's discussion of acute heart effects relies heavily on studies of questionable validity and fails to accurately represent the conclusions of some reports

OSHA addresses the issue of acute heart effects in the Proposed Rule at Section II.C.4.(d). (59 FR 15977-8)

In this section, OSHA argues that ETS exposure has certain acute effects, such as raising CO levels in the blood, increasing heart rate and blood pressure and affecting blood components that may be involved in atherosclerosis. Much of this section duplicates the claims in OSHA's immediately preceding

section on "Possible Mechanisms of Effect." OSHA again relies strongly on highly flawed studies, in particular, the 1978 Aronow study (Ex. 8-16, which is the same as Ex. 8-13) and the studies on platelets by Burghuber, et al. (Ex. 8-40) and Davis, et al. (Ex. 8-80).

One of OSHA's central points in this section is that exposure to ETS results in a significant increase in carboxyhemoglobin. It is odd that, in introducing this topic, OSHA cites the review and conclusions of the National Research Council (1986). In fact, the NRC report concluded that if background air has little or no carbon monoxide, then even upper estimates of what might be produced from ETS would "have a negligible effect on carboxyhemoglobin levels." (p. 128) Furthermore, the 1986 Surgeon General's Report, in addressing this same issue, concluded as follows: "Thus, small increments of carbon monoxide due to environmental tobacco smoke may be indistinguishable from that due to endogenous and non-tobacco-related sources." (p. 202)

OSHA also incorrectly describes that data in Guerin, et al. (Ex. 8-129) as indicating that it is common for workplace ETS exposure to be associated with significant increases in COHb levels. In point of fact, Ex. 8-129 concludes the opposite, noting that "studies which quantified the percentage COHb in nonsmokers show very little difference in nonsmokers who were or were not

exposed to ETS." (p. 160) Elsewhere in Ex. 8-129, a similar conclusion is reached, noting that nearly all CO in indoor environments arises from sources other than ETS.

> CO has been measured repeatedly in rooms where there is adequate ventilation, with and without cigarette smoking. In many cases, the difference in values is small, and is easily masked by either normal variation in the data or the precision of the analytical measurement. Studies which measure the concentration of COHb in both ETS-exposed and non-exposed subjects is consistent with environmental CO measurements, and have demonstrated no consistent significant differences in most indoor environments. The chief difficulty is interferences from other sources of CO, particularly cooking, heating, and vehicle exhaust. One author (Eatough, 1988) states that about 90% of all CO arises from sources other than ETS. (p. 177) (Ex. 8-129)

Other literature cited by OSHA in this section also does not provide substantial support for, and sometimes is, at best, remotely relevant to OSHA's claims of acute cardiovascular responses to ETS. For example, OSHA cites Ex. 3-38 to support its claim that ETS has acute effects in angina patients. However, Ex. 3-38 consists of materials from the state of Washington, Department of Labor and Industries, relating to a proposed indoor air regulation. It has no apparent relevance to the context in which OSHA cited it. On the same point, OSHA cites Milhorn (1989). (Ex. 8-222) But Milhorn (1989) is not a study of ETS. It is

primarily a review of behavioral issues related to nicotine, as they might be relevant to physicians' advice to their patients about smoking.

On the issue of potential cardiovascular responses in healthy people, OSHA cites Asano, et al. (1985) and McMurray, et al. (1985). (Exs. 8-18 and 8-17) Although these articles report minor changes in certain cardiovascular variables, such as heart rate, it is doubtful whether these have any physiological significance, even assuming that such responses were actually direct responses to ETS, rather than reflective of a psychological reaction to ETS exposure.

In supporting its claim that ETS exposure has acute effects on blood components, OSHA again cites Burghuber, et al. (Ex. 8-40) and Davis, et al. (Ex. 8-80), which as noted repeatedly above are very weak, especially relative to the scientific weight OSHA is urging them to carry.

OSHA claims that effects of ETS exposure "may be additionally aggravated by simultaneous exposure to other compounds." In support, OSHA cites Ex. 3-446, which consists of comments from a government employee's labor union, and appears to provide no substantive information on this issue. On this same point, OSHA cites a 1988 review by Eriksen, et al. (Ex. 8-99) This

is perplexing, since the conclusions in Ex. 8-99 generally track those in the 1986 National Research Council and Surgeon General's Reports, namely, that data on the issue of ETS exposure and cardiovascular effects are methodologically weak and unconvincing.

There are several reports and reviews, not considered or not adequately taken into account by OSHA, which have addressed the issue of potential cardiovascular responses to ETS. Selections from this literature are set forth in Part II.C. of this submission, indicating a sizeable body of scientific data and opinion questioning a role of ETS or of ETS constituents in acute cardiovascular effects.

OSHA's discussion of epidemiologic and experimental data does not adequately support claims of an increased risk of chronic heart effects associated with ETS exposure in the workplace; OSHA fails to critically review cited studies; OSHA misrepresents the nature of available data

OSHA addresses the issue of chronic heart effects in the Proposed Rule at Section II.C.4.(e). (59 FR 15978-9) Epidemiologic literature on this issue is also reviewed in the context of its risk assessment, at Section IV.B. (59 FR 15992)

In Section II.C.4.(e), OSHA provides a single paragraph discussion of the epidemiologic studies relating to ETS and heart

disease, coming to the conclusion that these studies indicate a "modest impact" of ETS exposure on heart disease, with relative risks in the range of 1.3 to 2.7.

OSHA cites the following epidemiological reports.

Ex. 8-85, Dobson, et al. (1991)
Ex. 8-120, Garland, et al. (1985)
Ex. 8-138, He, et al. (1989)
Ex. 8-139, Helsing, et al. (1988)
Ex. 8-142, Hirayama (1984)
Ex. 8-148, Hole, et al. (1989)
Ex. 8-154, Humble, et al. (1990)
Ex. 8-191, Lee, et al. (1986)
Ex. 8-277, Sandler, et al. (1989)
Ex. 8-295, Svendsen, et al. (1987)

Contrary to OSHA's claim, the 11 citations given by OSHA in support of its conclusion do not report a consistent association of ETS exposure, usually inferred from spousal smoking, and heart disease risk. In studies where questionnaire estimates were obtained concerning workplace exposure, the data are especially weak on the issue of a possible association of ETS exposure and heart disease risk.

OSHA's misleading use of the 11 epidemiologic reports it cites on ETS and heart disease is evident in the manner in which these reports are grouped in Table IV-2. (59 FR 15993) In two instances, once in the "Positive" column and once in the "Equivocal positive trend" column, OSHA cites the same study twice. In the "Positive" column, both Helsing, et al. (Ex. 8-139) and Sandler, et al. (Ex. 8-277) provide essentially the same data on ETS and heart disease. In the "Equivocal positive trend" column, Gillis, et al. (Ex. 8-122) report preliminary data later reported by Hole, et al. (Ex. 8-148) Listing all four reports, when only two studies are represented, gives the impression that more "positive" data are available than in fact might be the case.

It is of special interest that two of the studies on ETS and heart disease cited by OSHA as "positive" or with an "equivocal positive trend" reported data using questionnaire estimates of workplace exposure. However, neither of these studies provides data suggesting an association of workplace ETS exposure and increased heart disease risk.

One of the studies with workplace data, Dobson, et al. (Ex. 8-85), is categorized by OSHA in Table IV-2 (59 FR 15993) as "positive." However, in this study, for ETS exposure at work, the odds ratios and 95% confidence intervals were 0.95 (0.51-1.78) for men and 0.66 (0.17-2.62) for women. Dobson, et al. concluded:

"The odds ratios for passive smoking at work did not suggest increased risk." (p. 793)

In another report, categorized by OSHA as having an "equivocal positive trend," Svendsen, et al. (Ex. 8-295) collected a "limited amount" of data on workplace ETS exposure. Study participants were asked about the smoking habits of their coworkers. Comparing nonsmokers whose coworkers smoked to nonsmokers whose coworkers did not smoke, the following relative risks (with 95% confidence intervals) were reported for heart disease.

-- Coronary heart disease death - RR = 2.6 (CI 0.5-12.7)

-- Fatal or nonfatal coronary heart disease - RR = 1.4 (CI 0.8-2.5)

Svendsen, et al. also reported data on a potential joint effect of coworker smoking plus spousal smoking, for the endpoint fatal or nonfatal coronary heart disease. Relative to nonsmoking men, neither whose wives nor coworkers smoked, the following risks were reported.

-- Both wife and coworkers smoked - RR = 1.7 (CI 0.8-3.6)

-- Wife smoked, but coworkers did not - RR = 1.2 (CI 0.4-3.7)

-- Wife did not smoke, but coworkers did - RR = 1.0 (CI 0.5-1.9)

In sum, all relative risks pertaining to workplace ETS exposure (either alone or in combination with spousal smoking) were not statistically significant.

OSHA incorrectly lists Hirayama (Ex. 8-142) as a "positive" study in Table IV-2. (59 FR 15993) While one of Hirayama's tables (Table 5, p. 183 of Ex. 8-142) appears to contain a statistically significant risk ratio for one subgroup of nonsmoking women married to smokers, Hirayama did not report an overall relative risk. Using Hirayama's data, however, Lee (Lee, P.N., Environmental Tobacco Smoke and Mortality. Karger, New York, 1992) recently calculated this ratio to be a nonstatistically significant 1.15 (95% C.I.: 0.94-1.42). (Lee, 1992, p. 187)

Very little weight can be given to the He, et al. study (Ex. 8-138), since it is a minor Chinese-language report based on

only 34 heart disease cases. As noted previously, the Sandler, et al. (Ex. 8-277) report is not relevant since it repeats the data in Helsing, et al. (Ex. 8-139) Also, as noted, the Dobson, et al. report (Ex. 8-85), actually reported nonstatistically significant relative risks less than 1.0 insofar as workplace data are concerned. This leaves OSHA's conclusions on increased heart disease risk based on a single "positive" epidemiological study, Helsing, et al. (Ex. 8-139)

As is typical of ETS epidemiological studies, Helsing, et al. suffers from weaknesses, such as unreliable ETS exposure estimates, and failure to attempt to control for confounding factors. The issue of unreliable exposure estimates is a particular problem for Helsing, et al., because the smoking status data were collected in 1963 and then used to classify subjects during the 12 years following. Many changes probably occurred in smoking behavior during the subsequent 12-year follow-up. This concern was noted by the authors.

> All smoking data were obtained in the 1963 census, so no provision can be made for changes in smoking habits which we know took place as a result of publicity about health effects of smoking. (p. 921)

Other changes in the compositions of the households may have occurred during the follow-up period. Although the authors

assume that any changes might influence the ETS comparison groups randomly, this is mere speculation.

> We also have no data on changes in the household composition which may have occurred prior to or after 1963. Thus, we implicitly assume that any such changes occurred randomly in the population. (p. 921)

Although an attempt was made to adjust statistically for some potential heart disease risk factors (age, sex, etc.), no data were available on many potentially important risk factors for heart disease, such as diet, exercise, blood pressure and cholesterol.

> We have very little data on other risk factors for arteriosclerotic heart disease in the study population. . . . other factors such as diet and exercise might differ in families with and without smokers; we cannot ignore the possibility that such differences could influence our findings. (p. 921)

In sum, the epidemiological literature cited by OSHA as providing "positive" evidence of an ETS and heart disease association provides an extremely weak scientific basis for such a claim. After excluding incorrectly cited literature (Sandler, et al.; Hirayama), a small-scale foreign report of uncertain reliability (He, et al.) and research which, in fact, challenges a workplace ETS exposure/heart disease claim (Dobson, et al.), OSHA

is left with a single supporting citation (Helsing, et al.), which itself is highly flawed.

The problems with Helsing, et al. are particularly troublesome for OSHA's case, because OSHA's risk estimate for heart disease deaths associated with ETS (Section IV.D., 59 FR 15995-6), depends entirely on the Helsing, et al. data for its relative risks. OSHA ignores or glosses over the study's weaknesses relating to ETS exposure, classification of smoking status and confounding factors. Furthermore, without adequate foundation, OSHA states matter-of-factly that the Helsing, et al. study "can be generalized to the general public," conveniently failing to acknowledge that the Helsing, et al. study was performed in a single county in a single state in the U.S.

In addition to epidemiologic reports, OSHA also uncritically cites a number of laboratory and clinical reports or reviews, many of which were designed to examine active smoking and do not even relate to ETS. Other studies which purport to relate to ETS are cited by OSHA as fact without any serious attempt to evaluate their scientific validity.

For example, OSHA provides a substantial amount of detail concerning a recent study said to show that ETS exposure increases myocardial infarct size in rats and increases atherosclerosis in

rabbits. In this context, OSHA incorrectly describes a 1993 report by Zhu, et al. (Ex. 8-330) as relating to infarct size in rats, when, in fact, Ex. 8-330 is a rabbit study of atherosclerosis. The rat infarct study described by OSHA appears to be a 1994 report by Zhu, et al. (Zhu, B., Sun, Y., Sievers, R.E., Glantz, S.A., Parmley, W.W. and Wolfe, C.L., "Exposure to Environmental Tobacco Smoke Increases Myocardial Infarct Size in Rats," Circulation 89(3): 1282-1289, 1994.) Neither the 1994 Zhu, et al. report on rat infarcts, nor the report on atherosclerosis in rabbits cited by OSHA (Ex. 8-330) meet basic standards of scientific control. Both involve excessively high levels of smoke exposure, which was sidestream smoke, not ETS. The conditions of exposure also left a stress factor uncontrolled, which is particularly important in heart disease research.

To examine the 1994, Zhu, et al. report in more detail, it is clear that it is not even relevant to ETS. It apparently involved simultaneous exposure of groups of rats, up to 24 at a time, to extremely high levels of sidestream smoke, not ETS, in an unventilated exposure chamber. The average air levels of nicotine (1103 $\mu g/m^3$) and carbon monoxide (92 ppm) are several orders of magnitude higher than would be observed in even the most extreme human smoking situation. Moreover, a group of confined rats together in a chamber pumped full of smoke to the point where breathing was almost impossible is going to experience stress in

direct proportion to the extent of exposure. Any test for myocardial infarction is going to be influenced by such a stress factor. In short, the Zhu, et al. study is probably more of a study of stress than a study of ETS.

In an effort to support OSHA's claim that ETS adversely affects "blood components," OSHA denotes nearly half a column to a 1985 report by Olson. (Ex. 8-245) Olson reports that excessive exposure to intense levels of only weakly diluted sidestream smoke in rats can substantially elevate COHb levels. However, the Olson report did not even pertain to heart disease; it was a study of lung enzymes. It involved high concentrations of sidestream smoke, not ETS, which is a highly dilute mixture. Furthermore, it is clear that the exposure conditions were not relevant to COHb levels associated with ETS, when even literature cited by OSHA indicates that COHb levels in ETS-exposed nonsmokers are essentially indistinguishable from nonexposed nonsmokers. (Guerin, et al., Ex. 8-129, discussed under "Acute Effects.")

The Davis, et al. report (Ex. 8-80) on platelets and endothelial cells is again cited, despite its lack of an adequate control condition.

OSHA cites two Czechoslovakian reports to support a claim that ETS exposure affects cardiac cellular metabolism.

(Gvozdjakova, et al., 1984, Ex. 8-130; Gvozdjakova, et al., 1985, Ex. 8-131) Both of these studies are from the same laboratory and involve an experimental model in which rabbits were apparently exposed to mainstream cigarette smoke for periods of up to eight weeks. The authors claim that this smoke exposure adversely effected myocardial mitochonchial respiration. This is suggested as a mechanism underlying cardiomyopathy in smokers. Although the model involved "passive" inhalation of smoke by the rabbits, it is clear from the levels and nature of smoke delivery, and from the authors' explicit comments, that this research was intended to apply directly to heart disease in smokers, not to ETS.

Benowitz (1991) (Ex. 8-25) is cited several times to support claims about nicotine and carbon monoxide. This citation, however, does not deal with ETS. It is a review of nicotine in the context of smoking and delivery of nicotine via nicotine gum or via transdermal patches. Likewise, the Muscat, et al. (1991) report (Ex. 8-234) on lipid profiles deals with smokers, not ETS.

Leone, et al. (1991) (Ex. 4-196) is cited as support for a claim that CO decreases ventricular fibrillation threshold. The Leone, et al. report did not provide data on ventricular fibrillation, much less any data about CO and ventricular fibrillation in particular.

Conclusion

In conclusion, OSHA's discussion of cardiovascular effects is replete with incorrectly cited literature, misinterpreted or uncritically-examined studies and blatant errors as to the relevance of OSHA's citations to the claims advanced. Thus, OSHA has failed to make its case that ETS exposure in the workplace is associated with heart disease risk. The best available evidence is data on workplace ETS exposure and heart disease risk. To the extent that workplace ETS exposure data are available, an association with heart disease risk is not supported.

Part II: Additional Literature Ignored or Not Considered Adequately by OSHA

OSHA OMITS A NUMBER OF RELEVANT REVIEWS AND STUDIES FROM THE PROPOSED RULE; THESE REFERENCES FURTHER UNDERMINE CLAIMS THAT ETS EXPOSURE IN THE WORKPLACE IS ASSOCIATED WITH A SIGNIFICANT RISK OF HEART DISEASE

A. Literature reviews challenging claims of ETS-associated risk

The literature contains several literature reviews which conclude that a potential relationship of ETS exposure and heart disease has not been established. In view of the highly limited data on workplace ETS exposure, it is not surprising that none of these reviews provide conclusions specifically focusing on the workplace. However, these reviews do address broad problems with the ETS/heart disease data. If such data are generally inconclusive, then they are reasonably viewed as also specifically inconclusive in regard to the workplace. OSHA failed to recognize the conclusions of these reviews.

U.S. Department of Health and Human Services (1986)[1]

This review examined the available data and judged that "no firm conclusion" (p. 10) could be made regarding a possible relationship between ETS and heart disease.

Committee on Passive Smoking, Board on Environmental Studies and Toxicology (1986)[2]

This committee report stated that any potential heart disease risk related to ETS would be "difficult to detect or estimate reliably" from epidemiological studies, and would be "the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates." (p. 263)

Wexler, L.M. (1990)[3]

At a ETS conference held at McGill University in 1989, Lawrence Wexler, of the New York Medical College, concluded that recent data did not provide a basis for altering the earlier conclusions by the Surgeon General and National Research Council concerning ETS and cardiovascular disease.

> Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. (p. 139)

Weetman, D.F. and Munby, J. (1990)[4]

Two scientists from the University of Sunderland, United Kingdom, reviewed the literature on ETS and heart disease and presented their conclusions at an international conference on indoor air quality held in Lisbon, Portugal in April 1990.

> It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials are instigated, and some objective measure of degree of exposure can be devised. (p. 215)

Weetman, D.F. (1993)[5]

In a subsequent conference, which addressed a variety of reported risk factors for heart disease in nonsmokers, Professor Weetman again reviewed the ETS and heart disease issue. His review focused on the epidemiological literature, and emphasized that major flaws in the available studies made it impossible to draw conclusions as to any possible association of ETS exposure and heart disease.

> It is not possible to conclude that a risk to cardiovascular health has been established from the epidemiological studies considered in this paper. Each of the studies is flawed in at least one major way. If there are to be more studies, and the importance of cardiovascular diseases suggests there should be, one can only hope that they will be conducted in a careful and objective way. (pp. 134-135)

Thiery, J. and Cremer, P. (1990)[6]

Two physicians from the University of Munich, Germany, presented their conclusions at an international conference in Hungary in June 1990.

> Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data. (p. 6)

Armitage, A.K. (1991)[7]

In a 1991 book discussing a wide range of issues involving ETS, the literature on heart disease was reviewed by Alan Armitage, former director of toxicology of a major European research laboratory and head of pharmacology at the Tobacco Research Council Laboratories in the United Kingdom. He judged that the scientific data have not established an increased heart disease risk in nonsmokers exposed to ETS.

> It is clear that the evidence for a harmful effect of ETS in enhancing CHD [coronary heart disease] risk in non-smokers is not very convincing. . . . (p. 114)

Armitage, A.K. (1993)[8]

In a subsequent review in 1993, Armitage, writing as a consultant pharmacologist and toxicologist, expressed a similar evaluation of the ETS/heart disease literature.

On the current evidence a causal relationship between exposure to ETS and the development of CHD has not been proved. (p. 27)

Caldwell, A.D.S. (1993)[9]

Armitage's 1993 review appeared in the Journal of Smoking-Related Diseases. In an editorial in the same journal issue, A.D.S. Caldwell, the journal's managing editor, emphasized that the issue of confounding variables was of particular importance in the case of heart disease. This is because of the hundreds of factors reportedly associated with the disease. Caldwell observed that the numerous heart disease risk factors make it extremely difficult to make confident statements about a potential role of ETS.

> But assessing the impact of ETS is an exercise made hazardous by confounding variables lurking around every statistical corner. In the case of CHD, for example, some 300 risk factors have at some time or other been identified -- by what means is it possible to unravel these data and point the finger with any degree of confidence at ETS per se as a major causative element?

Lee, P.N. (1991)[10]

In 1991, Peter Lee, an independent British statistical consultant, published a critical analysis of the epidemiological literature relating to ETS exposure, cancer and heart disease. In the area of heart disease, he was particularly critical of the risk

assessments by Wells (1988) and Kawachi, et al. (1989). Both of these risk assessments concluded that ETS is associated with a large number of heart disease deaths annually. Lee challenged this conclusion, and agreed with the 1986 National Academy of Sciences and Surgeon General's reports, in that both considered the ETS/heart disease data inadequate.

> In the risk assessment by Wells, heart disease deaths formed 70% of the total. In that by Kawachi et al, they formed 89%. As noted above, in 1986 none of the major authorities considered that ETS had been shown to cause heart disease. Evidently Wells and Kawachi, in assuming that ETS causes heart disease, are jumping to a conclusion that a number of panels of distinguished scientists have not reached. While there are more data now than in 1986, it remains abundantly clear that the evidence still does not support this conclusion. (p. 199)

> Although it has been demonstrated above that the risk assessment for heart disease essentially rests on the results from two studies, both of which seem unreliable, a number of other general points can be made. First, there are a very large number of risk factors for heart disease. It is evident that adjustment for these factors in the studies has always been incomplete, and often seriously incomplete. Second, the extent of the association seen in some of these studies, which in some cases is close to that reported in relation to active smoking, is implausibly high when viewed against the extent of the association seen in relation to active smoking. Third, there is a major danger of publication bias. It is notable that the literature is still relatively sparse despite the numerous ongoing studies of heart disease and the fact that heart disease in a non-

> smoker is probably 50 times or so more common than lung cancer in a non-smoker. (p. 200)

Lee, P.N. (1992)[11]

In 1992, Peter Lee published a more detailed, book-length review of the epidemiological literature on ETS exposure in relation to mortality and several diseases. In his view, various weaknesses and biases in the data precluded the ability to draw any conclusion as to the potential association of ETS exposure and heart disease.

> Mainly because of the problems caused by the strong likelihood of severe publication bias, it cannot be concluded from the existing evidence that ETS is associated with heart disease. The present author understands that the American Cancer Society intends to publish within the next year or so findings related to ETS based on its second large prospective study. It is hoped that results from its first prospective study will also be released. Until there is such evidence, and hopefully also evidence from other studies involving substantial numbers of deaths from heart disease with good control of confounding and with evidence on ETS exposure from sources other than the spouse or in the home, it is certainly premature to come to any conclusions. (pp. 195-196)

Huber, G.L. Brockie, R.E. and Mahajan, V.K. (1992)[12]

Gary Huber, M.D., of the University of Texas Health Center, in collaboration with two other physicians, recently reviewed the literature relating to claims that ETS is associated

with increased heart disease risk. These authors described the epidemiological studies as "inconsistent" and considered the magnitude of the risks reported in these studies to be "within the range of 'background noise.'" Huber, et al. also emphasized the point that potential confounding variables have not been adequately controlled in studies of ETS exposure and heart disease.

> The studies should be viewed with healthy scientific skepticism because they have not been controlled adequately for numerous confounding factors potentially important to the development of these diseases. (p. 32)

Aviado, D.M. (1992)[13]

In 1992, Domingo Aviado, M.D., a consultant with Atmospheric Health Sciences in Short Hills, N.J., published an extensive review of environmental tobacco smoke in the context of heart disease in the workplace. He did not consider the data supportive of an association of workplace ETS exposure with heart disease, and emphasized the low levels of ETS constituents to which workers might be exposed.

> It is the opinion of this author that the available studies do not support a judgment that ETS exposure is associated with any form of occupation-related heart disease. Although ETS reportedly contains constituents that have been associated with occupational heart disease, the concentrations are so low that it is unlikely for any substance to attain the

> corresponding TLV (threshold limit value) in a work environment. (pp. 475-476)

Aviado, D.M. (1993)[14]

In 1993, Dr. Aviado again addressed this issue, concluding that "the available studies do not support a judgment that ETS exposure is associated with any form of occupation-related heart disease." (p. 130)

Crépat, G. (1992)[15]

G. Crépat, a scientist at the University of Dijon, France, reviewed the literature relating to ETS exposure and heart disease, in a presentation at an international indoor air quality meeting in Athens, in April 1992. He concluded that the relative risks for ETS and heart disease reported in epidemiologic studies have probably been overestimated and are not explained by the available "physiobiochemical" data.

> This suggests that mean RR [relative risk] of CHD due to ETS exposure calculated from available epidemiologic studies, has probably been overestimated as at the moment it cannot be explained by physiobiochemical changes caused by ETS in the body. (p. 440)

B. Literature emphasizing low levels of ETS constituents

One way to approach the question of ETS and heart disease is to examine the levels of ETS to which nonsmokers might be exposed. Reported levels of exposure to carbon monoxide may be particularly of interest in view of the potential role some authors have speculated it to have in heart disease. The literature provides many examples of reviews concluding that potential nonsmoker ETS or CO exposure levels are extremely low and not likely to be of physiological significance. The conclusions of several notable examinations of this issue are extracted below.

Adlkofer, F.X., Scherer, G., Von Meyerinck, L., Von Maltzan, Ch. and Jarczyk, L. (1989)[16]

> COHb in passive smokers rises only slightly above the normal physiological level so that it is difficult to differentiate from COHb-values measured in non-exposed non-smokers. (p. 185)

Cole, P. (1981)[17]

> Another source of CO is the inhalation of exhaled tobacco smoke and sidestream smoke from other smokers, called 'passive smoking'. In a City office adjacent to Barts, where smoking was allowed, we measured the COHb levels in 100 non-smokers working alongside active smokers. Again, the mean level was slightly up, 1.12%, but again the increase is hardly significant. Passive smoking, although undeniably unpleasant to some can hardly be described as a health hazard. The rise in COHb does not even approach that found in an

active smoker. In the same City office we measured COHb in a 100 active smokers at the same time. They showed a mean level of 5.5% with a maximum of 13%, a completely different picture. We have rarely found a known non-smoker to exceed a level of 2.5% COHb and most are much lower. (p. 76)

Gori, G.B. and Mantel, N. (1991)[18]

The daily levels of cigarette consumption compatible with no significantly increased risk for other diseases associated with active smoking appear to be of the same order as for lung cancer. Tables 4 and 5 report the analogous estimates for cardiovascular and respiratory disease mortality, with the implication that retained doses of ETS are unlikely to be associated with significant risk elevations for such disease as well. (p. 96)

Table 4 in the paper summarizes data from epidemiologic studies of smoking and heart disease, and provides the "maximum levels of daily cigarette consumption at which risk for coronary heart disease mortality in male smokers may not be significantly increased from the risk of nonsmokers." The maximum levels are in the range of 1.5-4.5 cigarettes per day. By contrast, Gori and Mantel calculate that the average ETS-exposure for a nonsmoker is "less than one cigarette over the course of 1 year."

Together, these considerations suggest that the lung cell doses for average ETS-exposed nonsmokers are probably between 1/10,000 and 1/100,000 of equivalent cell doses for average mainstream active smokers. In practical

> terms, this implies an annual retained dose of tobacco smoke components equivalent to far less than the dose from the active smoking of one cigarette somehow evenly dispersed over a 1-year period. (p. 94)

<u>Malmfors, T., Thorburn, D. and Westlin, A. (1989)</u>[19]

This is a study of the air quality in passenger aircraft, focusing on components related to ETS. Although no potential health effects were measured, the report emphasizes the low levels of ETS-related components, and observes these are unlikely to have an important cardiovascular significance. It is also noted that the nicotine and carbon monoxide levels in aircraft cabins are well below the standards set by OSHA.

> It can be seen that the nicotine concentrations found in the present study are roughly one-tenth of the standard for the working environment set by OSHA. The concentration of carbon monoxide is also about one-tenth of the standard for general indoor air and even less for the working environment. (p. 623)

> From this comparison it appears that the quality of the aircraft cabin air in the present study is satisfactory and better for factors related to ETS - nicotine and carbon monoxide - than for carbon dioxide and relative humidity. (p. 624)

> Any effects on the cardiovascular system would have been mostly unnoticed in healthy individuals, because there are no known direct effects of ETS on the cardiovascular system beyond the formation of carboxyhemoglobin. The latter is so minimal that it will not affect the cardiovascular function. (p. 626)